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Dirhodium(II) tetraacetate catalysed reactions of diazo thioamides: isolation and cycloaddition of anhydro-4-hydroxy-1,3-thiazolium hydroxides (thioisomünchnones), an approach to analogues of dehydrogliotoxin

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Received 21st May 2003, Accepted 23rd June 2003
First published as an Advance Article on the web 9th July 2003

Dirhodium(II) tetraacetate catalysed reaction of the indoline diazo thioamide **8** gives the thioisomünchnone **9**, a stable characterisable solid. This masked thiocarbonyl ylide undergoes 1,3-dipolar cycloaddition with *N*-methylmaleimide and maleic anhydride to give the *exo*-cycloadducts **10** and **11**, characterised by *X*-ray crystallography. The thioisomünchnone **18**, derived from diazo thioamide **17**, is an extremely stable crystalline mesoionic system which can be characterised by *X*-ray crystallography but fails to undergo intramolecular cycloaddition. The related thioisomünchnone **19** can be generated by reaction of indoline-2-thione **7** with bromoacetyl chloride in the presence of triethylamine, and undergoes cycloaddition to give adducts **20** and **21**.

Introduction

Epidithiodiketopiperazines are a class of fungal secondary metabolites that are characterised by the presence of a disulfide bridging the 3,6-positions of the piperazine-2,5-dione ring. As a class, these compounds display a range of biological activity,[1,2] and interest has been heightened by the fact that gliotoxin **1**, one of the best known epidithiodiketopiperazines, possesses significant anticancer effects.[1,2] Our own interest in the area was stimulated by the report that KT7595 **3**, a simple analogue of dehydrogliotoxin **2**, is a potent inhibitor of ras farnesylation,[3] and we initiated a programme to investigate a range of structures **4** which retained the biologically important sulfur bridge but replace the diketopiperazine ring (Fig. 1).

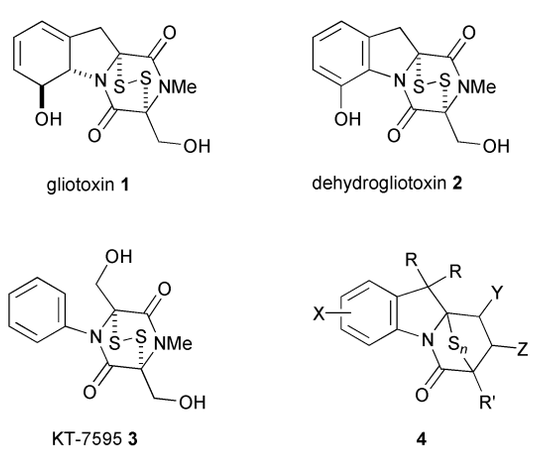
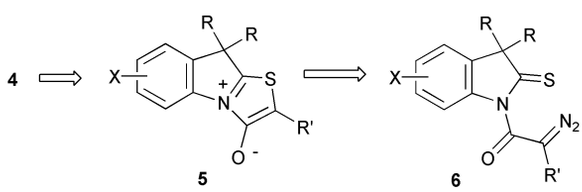


Fig. 1

The proposed strategy for the synthesis of the dehydrogliotoxin analogues **4** involves the cycloaddition of an anhydro-4-hydroxy-1,3-thiazolium-4-hydroxide (thioisomünchnone) derivative **5**, a mesoionic system which contains a masked thiocarbonyl ylide 1,3-dipole (Scheme 1). Potts and co-workers,[4–9] and more recently the Padwa group,[10–15] have extensively investigated the cycloaddition reactions of thioisomünchnones, generating the mesoionic system by the reaction of a thioamide with an α-halo acid halide followed by treatment with triethylamine to generate the 1,3-dipole.[16,17] However, by analogy with the oxygen analogues, isomünchnones, which are efficiently obtained by the dirhodium(II) catalysed reaction of diazo imides,[18,19] one would expect thioisomünchnones to be similarly prepared from the corresponding diazo thioamide. Although there are isolated examples of this approach,[9,10,12,14] the formation of thioisomünchnones by the interaction of rhodium carbenoids derived from diazo thioamides has not been extensively studied, and therefore we decided to investigate the synthesis of 1,3-dipoles **5** from the corresponding diazo thioamides **6** (Scheme 1).



Scheme 1

Results and discussion

The starting material for our study was the known 3,3-dimethylindoline-2-thione **7**,[20] prepared in four steps from oxindole (see Experimental section), which was treated with sodium hydride and ethyl 2-diazomalonyl chloride[21] to give the diazo thioamide **8** in 61% yield. When *n*-butyllithium was used as base an isomeric diazo compound, presumably an indolenine as a result of acylation on sulfur, was isolated.

Initially the dirhodium(II) catalysed reaction of diazo thioamide **8** was carried out in the presence of *N*-methylmaleimide, maleimides being widely used cycloaddition partners for both carbonyl- and thiocarbonyl-ylides. Thus the diazo compound **8** was added to a mixture of *N*-methylmaleimide and a catalytic amount of dirhodium(II) tetraacetate in toluene at 90 °C. This gave three products, two of which were clearly the *exo*/*endo* cycloadducts formed by 1,3-dipolar cycloaddition to the intermediate thioisomünchnone thiocarbonyl ylide dipole **9**. The cycloadducts were formed in 75% yield with the major product (ratio ~ 7 : 1) being the *exo*-adduct **10** (66%) (Scheme 2), the structure of the adduct being confirmed by *X*-ray crystallo-

DOI: 10.1039/b305698h

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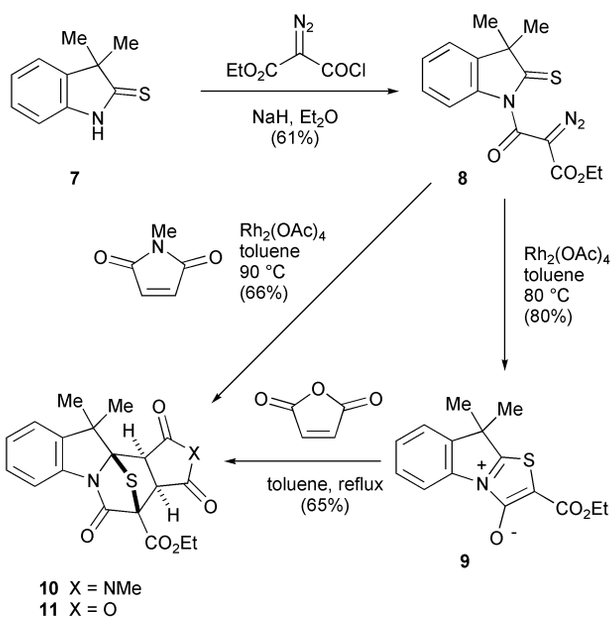
Table 1 Crystal data

	Compound **10**	Compound **11**	Compound **18**
Empirical formula	$C_{20}H_{20}N_2O_5S$	$C_{19}H_{17}NO_6S$	$C_{17}H_{17}NO_3S$
Formula weight	400.44	387.40	315.38
Temperature	293(2) K	293(2) K	293(2) K
Wavelength	1.54178 Å	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	*P*2(1)/*c*	*P*2(1)/*n*	*P*2(1)/*c*
Unit cell dimensions	$a = 14.396(3)$ Å $\alpha = 90°$ $b = 8.9008(18)$ Å $\beta = 105.83(3)°$ $c = 15.043(3)$ Å $\gamma = 90°$	$a = 7.8459(7)$ Å $\alpha = 90°$ $b = 9.6884(9)$ Å $\beta = 96.467(2)°$ $c = 24.179(2)$ Å $\gamma = 90°$	$a = 8.48(4)$ Å $\alpha = 90°$ $b = 18.39(9)$ Å $\beta = 99.58(5)°$ $c = 10.41(5)$ Å $\gamma = 90°$.
Volume	1854.4(6) Å^3	1826.3(3) Å^3	1601(13) Å^3
Z	4	4	4
Density (calculated)	1.434 Mg m^{-3}	1.409 Mg m^{-3}	1.309 Mg m^{-3}
Absorption coefficient μ	1.865 mm^{-1}	0.214 mm^{-1}	0.214 mm^{-1}
F(000)	840	808	664
Crystal size	0.2 × 0.2 × 0.1 mm^3	0.15 × 0.1 × 0.1 mm^3	0.15 × 0.1 × 0.1 mm^3
Reflections collected	2816	7637	6390
Independent reflections	2696 [*R*(int) = 0.0215]	2589 [*R*(int) = 0.0486]	2230 [*R*(int) = 0.0977]
Absorption correction	Empirical	Sadabs	Sadabs
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2696/0/254	2589/0/245	2230/1/200
Goodness-of-fit on F^2	1.033	0.925	0.976
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0454$, $wR2 = 0.1230$	$R1 = 0.0456$, $wR2 = 0.1062$	$R1 = 0.0654$, $wR2 = 0.1506$
R indices (all data)	$R1 = 0.0627$, $wR2 = 0.1358$	$R1 = 0.0926$, $wR2 = 0.1253$	$R1 = 0.1630$, $wR2 = 0.1889$
Extinction coefficient	0.0038(6)	0.0020(10)	0.0018(16)



Scheme 2

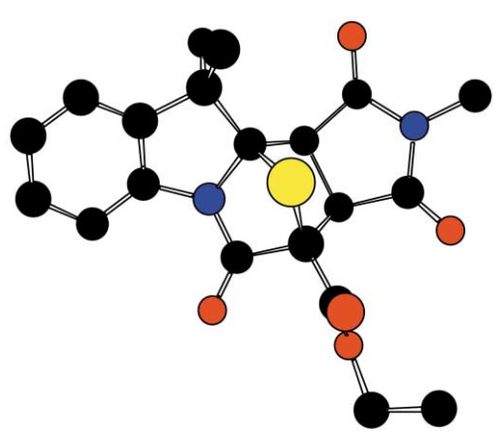


Fig. 2

graphy (Fig. 2, Table 1). The third product (19% yield) was identified as the thioisomünchnone **9** itself. Indeed when the maleimide dipolarophile was omitted from the reaction mixture, thioisomünchnone **9** could be isolated in 80–85% yield. The mesoionic system **9** is a stable yellow solid that could be fully characterised. As far as we are aware, of the previous investigations into the decomposition of related diazo thioamides,[9,10,12,14] only one resulted in the isolation of the intermediate thioisomünchnones as stable characterisable solids.[9]

As expected, the thioisomünchnone **9** reacted with the dipolarophile maleic anhydride upon heating to give the corresponding cycloadduct, *exo*-adduct **11** in 65% yield, with none of the corresponding *endo*-adduct being isolated. The cycloadduct **11**, the structure of which was confirmed by *X*-ray crystallography (Fig. 3, Table 1), was also formed by heating the diazo thioamide **8** in the presence of maleic anhydride and dirhodium(II) tetraacetate. However, acyclic dipolarophiles such as dimethyl maleate, phenyl vinyl sulfoxide, dimethyl acetylenedicarboxylate and α-chloroacrylonitrile all failed to react, suggesting that the masked 1,3-dipole **9** was too stable to react with all but the most reactive cyclic dipolarophiles.

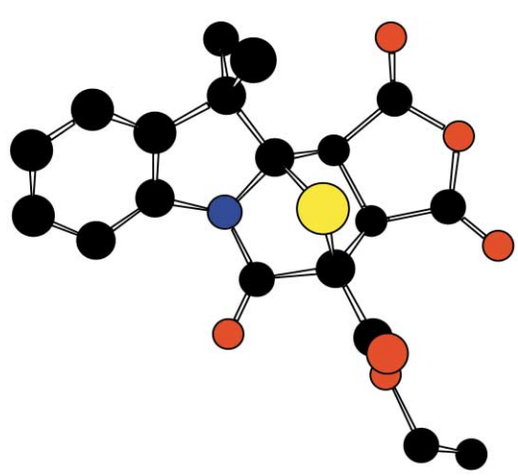
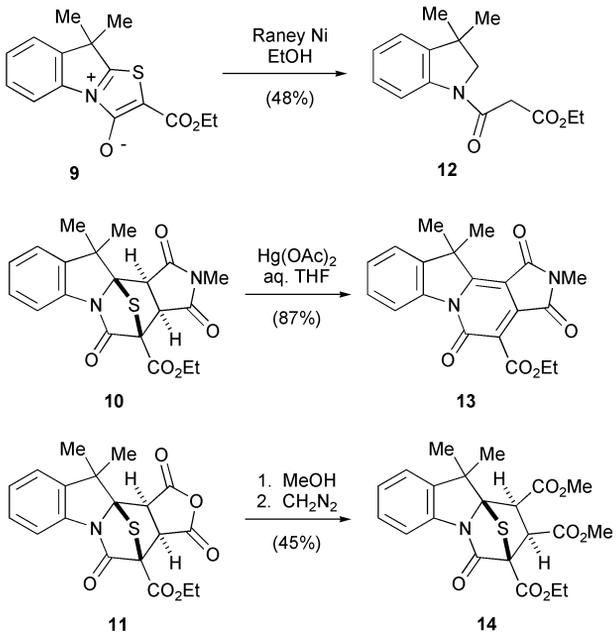


Fig. 3

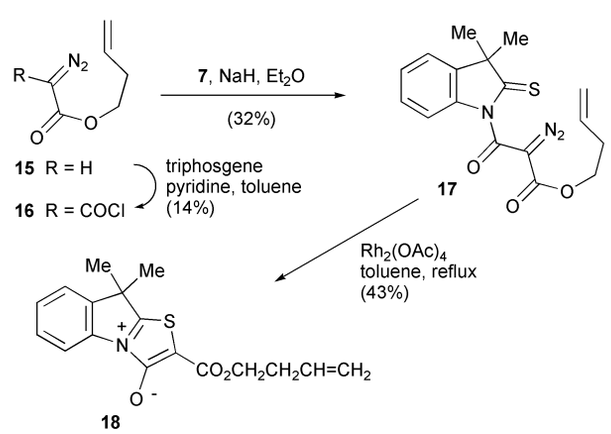
Upon treatment with Raney nickel, the thioisomünchnone **9** underwent desulfurisation to give the indoline **12** in modest yield. Likewise reaction of the cycloadduct **10** with mercury(II) acetate resulted in an aromatising desulfurisation to give the tetracyclic pyridone **13** in excellent yield (Scheme 3). The maleic anhydride adduct **11** underwent ring opening of the anhydride



Scheme 3

with methanol to give, after reaction of the resulting acid-ester with diazomethane, the diester **14**.

Given the apparent unreactivity of the thioisomünchnone **9** in intermolecular 1,3-dipolar cycloaddition reactions, an intramolecular cycloaddition reaction of the thioisomünchnone dipole was investigated. To this end, the known diazoester **15**[22] was treated with triphosgene to give the diazo acid chloride **16** in low yield, reaction of which with the indolinethione **7** gave the diazo thioamide **17** (Scheme 4). Treatment of **17** with a catalytic amount of dirhodium(II) tetraacetate in toluene at reflux gave the thioisomünchnone **18**, isolated in 43% yield after chromatography and crystallisation. The mesoionic system **18** is extremely stable and failed to undergo intramolecular dipolar cycloaddition even at higher temperatures (xylene at reflux). The structure of thioisomünchnone **18** was firmly established by *X*-ray crystallography (Fig. 4, Table 1), which showed the bond lengths around the five-membered ring to be similar to related mesoionic systems.[23]



Scheme 4

The inability of the thioisomünchnone **18** to undergo intramolecular cycloaddition provided further evidence of the stability of this particular anhydro-4-hydroxy-1,3-thiazolium hydroxide (thioisomünchnone), and therefore we investigated the corresponding 1,3-dipole **19** which lacks the electron-withdrawing ester group. Attempts to prepare the thioisomünchnone by way of 1-diazoacetyl-3,3-dimethyl-2,3-dihydroindole-2-thione failed due to the instability of the diazo compound, and therefore a more conventional approach using bromoacetyl chloride was adopted.[8,14] Thus the dipole was generated by the reaction of indoline-2-thione **7** with bromoacetyl chloride in the presence of triethylamine. Although the thioisomünchnone **19** was not isolable, it underwent cycloaddition with both *N*-methylmaleimide and dimethyl maleate to give the corresponding cycloadducts **20** and **21** in modest yield (Scheme 5).

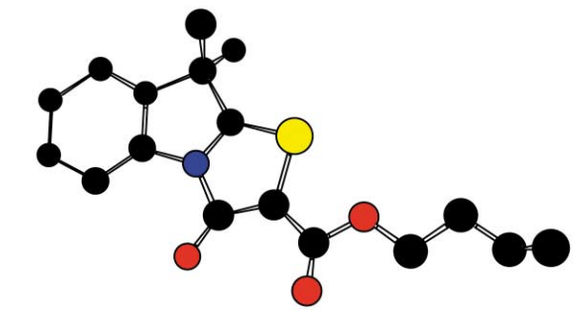
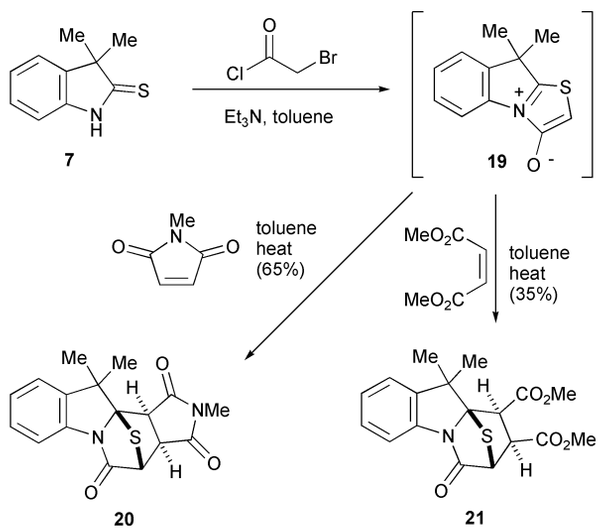


Fig. 4



Scheme 5

In conclusion, we have shown that dirhodium(II) catalysed reactions of appropriate diazo thioamides provide a good route to mesoionic thioisomünchnones, comparable to the corresponding route to their oxygen counterparts. The indole-derived thioisomünchnones are isolable stable compounds that can undergo the expected 1,3-dipolar cycloaddition reaction with reactive dipolarophiles to give fused thiazoloindoles, useful intermediates for the synthesis of analogues of dehydrogliotoxin.

Experimental

For general experimental details, see ref. 24.

tert-Butyl 2-oxo-2,3-dihydroindole-1-carboxylate

Oxindole (8.73 g, 0.066 mol) was dissolved in dry THF (300 ml) under nitrogen. Sodium carbonate (34.8 g, 0.328 mol) and Boc_2O (35.8 g, 0.164 mol) were added and the resulting mixture was stirred at room temperature for 24 h. After this time the reaction mixture was filtered and evaporated *in vacuo*. The resulting orange oil was purified by flash chromatography eluting with hexane–ethyl acetate (2⟶30%) to give the title compound (15.3 g, 74%) as a colourless solid, mp 65–68 °C (from hexane) (lit.,[25] mp 67 °C); δ_H (300 MHz; $CDCl_3$) 7.77 (1 H, d, *J* 8.0), 7.26 (2 H, m), 7.12 (1 H, t, *J* 7.4), 3.63 (2 H, s), 1.64 (9 H, s); δ_C (100 MHz; $CDCl_3$) 172.8 (C), 149.0 (C), 140.9 (C), 127.9

(CH), 124.03 (CH), 124.02 (CH), 123.1 (C), 114.9 (CH), 84.1 (C), 36.4 (CH_2), 28.0 (Me).

tert-Butyl 3,3,-dimethyl-2-oxo-2,3-dihydroindole-1-carboxylate

tert-Butyl 2-oxo-2,3-dihydroindole-1-carboxylate (16.7 g, 71.6 mmol) was dissolved in dry THF (175 ml) under nitrogen. Methyl iodide (13.5 ml, 214.8 mmol) was added and the mixture cooled on ice. Sodium hydride (60%; 6.3 g, 157.5 mmol) was added portionwise over 0.75 h maintaining the internal temperature below 10 °C. After complete addition the reaction mixture was stirred for a further 3 h before water (500 ml) was added. The resulting solution was then extracted into dichloromethane (4 × 100 ml), the combined organic extracts washed with saturated brine (2 × 200 ml), and dried further over Na_2SO_4. Removal of the solvent *in vacuo* gave a red solid which was purified by chromatography on silica eluting with light petroleum–ether (4 : 1) to give the *title compound* (12.5 g, 67%) as a colourless solid, mp 45–46 °C (from ethyl acetate–light petroleum); (Found: C, 69.0; H, 7.5; N, 5.3. $C_{15}H_{19}NO_3$ requires C, 68.9; H, 7.3; N, 5.4%); ν_{max} (KBr)/cm^{-1} 2980, 1772, 1730, 1608, 1481, 1348, 1254, 1149, 779; δ_H (300 MHz; $CDCl_3$) 7.85 (1 H, d, *J* 8.2), 7.33–7.13 (3 H, m), 1.66 (9 H, s), 1.43 (6 H, s); δ_C (75.5 MHz; $CDCl_3$) 179.8 (C), 149.5 (C), 138.3 (C), 134.5 (C), 127.9 (CH), 124.5 (CH), 122.2 (CH), 115.0 (CH), 84.3 (C), 44.5 (C), 28.1 (Me), 25.3 (Me); *m*/*z* (CI) 279 (M + NH_4, 100%), 262 (59).

3,3-Dimethyl-1,3-dihydroindol-2-one

tert-Butyl 3,3,-dimethyl-2-oxo-2,3-dihydroindole-1-carboxylate (8.41 g, 32.3 mmol) was dissolved in dichloromethane (60 ml) and cooled to 0 °C. TFA (30 ml) was added dropwise and the resulting mixture was stirred at 0 °C for 0.5 h. After this time the mixture was evaporated *in vacuo* and the residue purified by flash chromatography on silica eluting with light petroleum–ethyl acetate (3 : 1) to give the title compound (5.11 g, 98%) as a pale brown solid, mp 149–151 °C (from ethyl acetate) (lit.,[26] mp 152–153 °C); δ_H (300 MHz; $CDCl_3$) 9.42 (1 H, br s), 7.21 (2 H, m), 7.02 (2 H, m), 1.42 (6 H, s); δ_C (75.5 MHz; $CDCl_3$) 184.6 (C), 140.0 (C), 136.2 (C), 127.6 (CH), 122.5 (CH), 122.4 (CH), 110.0 (CH), 44.7 (C), 24.3 (Me).

3,3-Dimethyl-1,3-dihydroindole-2-thione 7

3,3-Dimethyl-1,3-dihydroindol-2-one (1.64 g, 10.2 mmol) was dissolved in dry toluene (20 ml) under nitrogen. Lawesson's reagent (2.17 g, 5.2 mmol) was added and the reaction mixture heated at reflux for 1.5 h. After this time the reaction mixture was allowed to cool and poured into water (75 ml). The organic layer was separated and the aqueous extracted with ether (3 × 50 ml). The combined organic layers were washed with saturated brine (2 × 50 ml) and dried further over Na_2SO_4. Removal of the solvents *in vacuo* gave a pale orange solid which was purified by flash chromatography on silica eluting with hexane–ethyl acetate (5⟶25%) to give the title compound **7** (1.34 g, 91%) as a pale yellow solid, mp 107–108 °C (from ethanol) (lit.,[20] mp 109–110 °C); δ_H (300 MHz; $CDCl_3$) 10.79 (1 H, br s), 7.27 (2 H, m), 7.16 (1 H, t, *J* 7.1), 7.08 (1 H, d, *J* 7.7), 1.47 (6 H, s); δ_C (75.5 MHz; $CDCl_3$) 214.2 (C), 141.3 (C), 140.7 (C), 127.9 (CH), 124.1 (CH), 123.1 (CH), 110.3 (CH), 55.3 (C), 27.7 (Me).

Ethyl 2-diazo-3-(3,3-dimethyl-2-thioxo-2,3-dihydroindol-yl)-3-oxopropanoate 8

3,3-Dimethyl-1,3-dihydroindole-2-thione **7** (1.13 g, 6.4 mmol) was dissolved in dry ether (30 ml) under nitrogen and cooled to 0 °C. Sodium hydride (60%, 282 mg, 7.0 mmol) was added and the resulting mixture stirred to room temperature over 10 min. Ethyl diazomalonyl chloride[21] (1.47 g, 8.3 mmol) was added in one portion and the reaction mixture stirred for an additional 1 h after which time saturated brine (50 ml) was added. The organic layer was separated and the aqueous extracted with ether (2 × 30 ml). The combined ethereal layers were further dried over Na_2SO_4, filtered and evaporated *in vacuo*. The resulting yellow oil was purified by flash chromatography on silica eluting with light petroleum–ether (85 : 15) to give *diazothioamide* **8** (1.24 g, 61%) as a yellow oil, (Found: M + Na^+, 340.0733. $C_{15}H_{15}N_3O_3S$ + Na requires 340.0732); ν_{max} (film)/cm^{-1} 2976, 2927, 2143, 1732 (br), 1678 (br), 1460, 1352, 1236, 1136, 1037, 752; δ_H (400 MHz; $CDCl_3$) 7.22 (4 H, m), 4.23 (2 H, q, *J* 7.1), 1.50 (6 H, s), 1.24 (3 H, t, *J* 7.1); δ_C (75.5 MHz; $CDCl_3$) 214.1 (C), 163.4 (C), 159.0 (C), 140.8 (C), 139.3 (C), 127.9 (CH), 125.0 (CH), 123.2 (CH), 111.3 (CH), 75.2 (C), 62.1 (CH_2), 56.2 (C), 28.5 (Me), 14.2 (Me); *m*/*z* (EI) 289 (M–N_2, 93%), 243 (74), 217 (95), 202 (57), 177 (76), 176 (89), 162 (59), 161 (100).

N-Methylmaleimide cycloadduct 10

Diazothioamide **8** (195 mg, 0.62 mmol) in dry toluene (3.5 ml) was added dropwise over a period of 20 min to a solution of *N*-methylmaleimide (75 mg, 0.68 mmol), dirhodium(II) tetraacetate (cat 1.4 mg) in dry toluene (2 ml) at 90 °C. The resulting solution was stirred for an additional 2 h, allowed to cool and filtered. Evaporation of the solvent gave a brown solid which was purified by chromatography on silica eluting with light petroleum–ethyl acetate (10⟶50%) to give (i) the *exo-cycloadduct* **10** (163 mg, 66%) as colourless prisms, mp 189–190 °C (from ethyl acetate); (Found: C, 59.7; H, 4.8; N, 6.6. $C_{20}H_{20}N_2O_5S$ requires C, 60.0; H, 5.0; N, 7.0%); ν_{max} (KBr)/cm^{-1} 2966, 2951, 1784, 1729 (br), 1707 (br), 1481, 1435, 1383, 1356, 1311, 1286, 1109, 1030, 769; δ_H (400 MHz; $CDCl_3$) 7.50 (1 H, d, *J* 7.6), 7.23 (2 H, m), 7.12 (1 H, t, *J* 6.9), 4.39 (2 H, q, *J* 7.1), 4.09 (1 H, d, *J* 6.8), 3.95 (1 H, d, *J* 6.8), 3.04 (3 H, s), 1.70 (3 H, s), 1.50 (3 H, s), 1.30 (3 H, t, *J* 7.1); δ_C (100 MHz; $CDCl_3$) 172.7 (C), 172.3 (C), 170.1 (C), 163.0 (C), 139.4 (C), 138.4 (C), 128.1 (CH), 125.0 (CH), 122.1 (CH), 114.1 (CH), 92.3 (C), 71.9 (C), 63.1 (CH_2), 55.6 (CH), 48.9 (CH), 44.4 (C), 28.5 (Me), 25.6 (Me), 22.8 (Me), 14.0 (Me); *m*/*z* (EI) 400 (M^+, 33%), 299 (29), 289 (100), 243 (42); (ii) the *endo-cycloadduct* (22 mg, 9%) as pale brown plates, mp 181–182 °C (from ethyl acetate); (Found: C, 60.1; H, 5.1; N, 6.5. $C_{20}H_{20}N_2O_5S$ requires C, 60.0; H, 5.0; N, 7.0%); ν_{max} (KBr)/cm^{-1} 2958, 2927, 1782, 1745 (br), 1713 (br), 1483, 1431, 1394, 1306, 1232, 1090, 978, 766; δ_H (400 MHz; $CDCl_3$) 7.41 (1 H, d, *J* 7.9), 7.17 (3 H, m), 4.31 (3 H, m), 4.19 (1 H, d, *J* 8.4), 2.75 (3 H, s), 1.97 (3 H, s), 1.45 (3 H, s), 1.40 (3 H, t, *J* 7.1); δ_C (100 MHz; $CDCl_3$) 172.3 (C), 170.6 (C), 163.7 (C), 161.9 (C), 141.2 (C), 134.7 (C), 128.3 (CH), 125.6 (CH), 122.6 (CH), 112.4 (CH), 92.1 (C), 69.0 (C), 63.2 (CH_2), 56.3 (CH), 52.8 (CH), 43.6 (C), 32.4 (Me), 25.1 (Me), 22.3 (Me), 14.1 (Me); *m*/*z* (EI) 400 (M^+, 22%), 368 (39), 295 (87), 289 (50), 224 (70); and (iii) the *thioisomünchnone* **9** (34 mg, 19%), data given below.

Thioisomünchnone 9

Diazothioamide **8** in toluene was treated with dirhodium(II) tetraacetate at 80 °C for 1.5 h. Evaporation of the solvent and chromatography on silica eluting with ethyl acetate gave the *title compound* (80–85%) as an amorphous yellow solid, mp 178–179 °C (from ethanol); (Found: C, 62.2; H, 5.1; N, 4.6. $C_{15}H_{15}NO_3S$ requires C, 62.3; H, 5.2; N, 4.8%); (Found: 2M + H^+, 579.1639. $C_{30}H_{30}N_2O_6S_2$ + H requires 579.1624); ν_{max} (KBr)/cm^{-1} 2989, 2970, 1681, 1662, 1581, 1467, 1438, 1374, 1340, 1188, 1070, 761; δ_H (300 MHz; $CDCl_3$) 8.40 (1 H, d, *J* 7.4), 7.45 (3 H, m), 4.35 (2 H, d, *J* 7.2), 1.65 (6 H, s), 1.37 (3 H, t, *J* 7.2); δ_C (75.5 MHz; $CDCl_3$) 173.2 (C), 163.2 (C), 157.1 (C), 142.9 (C), 138.3 (C), 129.1 (CH), 127.9 (CH), 122.6 (CH), 115.7 (CH), 91.4 (C), 60.5 (CH_2), 49.0 (C), 27.1 (Me), 14.7 (Me); *m*/*z* (FAB) 601 (2M + Na, 61%), 579 (2M + H, 14), 312 (100) (M + Na), 290 (28), 244 (86).

Maleic anhydride cycloadduct 11

To dry toluene (6 ml) was added maleic anhydride (64.4 mg, 0.66 mmol) and thioisomünchnone **9** (190 mg, 0.66 mmol) and the resulting mixture heated at reflux overnight. The solvent was removed *in vacuo* and the resulting brown solid recrystallised from dry ethyl acetate–light petroleum to give the *title compound* (166 mg, 65%) as a single stereoisomer; colourless prisms, mp 198–200 °C (from ethyl acetate–light petroleum); (Found: C, 58.8; H, 4.2; N, 3.4. $C_{19}H_{17}NO_6S$ requires C, 58.9; H, 4.4; N, 3.6%); (Found: M + NH_4^+, 405.1115. $C_{19}H_{17}NO_6S$ + NH_4 requires 405.1120); ν_{max} (KBr)/cm^{-1} 2974, 2937, 2875, 1853, 1784, 1768, 1674, 1481, 1315, 1205, 1103, 1026, 938, 741; δ_H (300 MHz; $CDCl_3$) 7.54 (1 H, d, *J* 7.7), 7.31–7.17 (3 H, m), 4.45 (3 H, m), 4.29 (1 H, d, *J* 7.4), 1.73 (3 H, s), 1.60 (3 H, s), 1.39 (3 H, t, *J* 7.1); δ_C (100 MHz; $CDCl_3$) 168.9 (C), 166.15 (C), 166.10 (C), 162.2 (C), 139.0 (C), 137.9 (C), 128.4 (CH), 125.4 (CH), 122.3 (CH), 114.2 (CH), 92.4 (C), 71.8 (C), 63.6 (CH_2), 55.1 (CH), 50.3 (CH), 44.6 (C) 28.3 (Me), 23.2 (Me), 14.0 (Me); *m*/*z* 405 (M + NH_4, 94%), 388 (MH^+, 17), 344 (26), 284 (100), 160 (48), 146 (87).

Ethyl 3-(3,3-dimethyl-2,3-dihydroindol-yl)-3-oxopropanoate 12

Thioisomünchnone **9** (53 mg, 0.18 mmol) was dissolved in ethanol (1 ml). W-2 Raney nickel (xs, 0.5 ml) was added and the resulting mixture stirred at 75 °C for 0.5 h. After the consumption of the starting material, the reaction mixture was filtered and the filtrate evaporated to give a colourless oil which was purified by chromatography on silica eluting with light petroleum–ethyl acetate (85 : 15) to give *indoline* **12** (23 mg, 48%) as a colourless oil, (Found: MH^+, 262.1447. $C_{15}H_{19}NO_3$ + H requires 262.1443); δ_H (400 MHz; $CDCl_3$) 8.19 (1 H, d, *J* 8.1), 7.26–7.06 (3 H, m), 4.25 (2 H, q, *J* 7.1), 3.81 (2 H, s), 3.54 (2 H, s), 1.40 (6 H, s), 1.31 (3 H, t, *J* 7.1); δ_C (100 MHz; $CDCl_3$) 167.1 (C), 163.7 (C), 141.2 (C), 140.6 (C), 127.8 (CH), 124.5 (CH), 121.8 (CH), 117.3 (CH), 63.2 (CH_2), 61.6 (CH_2), 44.0 (CH_2), 40.4 (C), 28.4 (Me), 14.1 (Me); *m*/*z* (EI) 261 (M^+, 42%), 246 (16), 174 (44), 146 (56), 132 (100).

Pyridone 13

Cycloadduct **10** (30 mg, 0.075 mmol) was dissolved in THF (0.5 ml) to which a solution of mercury(II) acetate (24.4 mg, 0.075 mmol) in water (0.5 ml) was added in one portion. The resulting mixture was stirred at room temperature for 0.5 h, after which time ethyl acetate (5 ml) was added. The organic layer was separated and dried by extraction with saturated brine (2 × 5 ml) and standing over anhydrous sodium sulfate. Subsequent filtration and removal of the solvent *in vacuo* gave a pale yellow gum which was purified by chromatography on silica eluting with light petroleum–ethyl acetate (4 : 1) to give the *title compound* (24 mg, 87%) as pale yellow prisms, mp 250–251 °C (from ethyl acetate–light petroleum); (Found: C, 65.4; H, 4.8; N, 7.5. $C_{20}H_{18}N_2O_5$ requires C, 65.6; H, 5.0; N, 7.7%); (Found: MH^+, 367.1290. $C_{20}H_{18}N_2O_5$ + H requires 367.1294); ν_{max} (KBr)/cm^{-1} 3014, 2983, 2972, 2936, 1778, 1745, 1716, 1662, 1656, 1624, 1595, 1437, 1383, 1259, 1146, 1092, 1041, 769, 750; δ_H (400 MHz; $CDCl_3$) 8.74 (1H, dd, *J* 8.0, 0.9), 7.47–7.26 (3H, m), 4.53 (2H, q, *J* 7.2), 3.19 (3H, s), 1.60 (6H, s), 1.54 (3H, t, *J* 7.2); δ_C (100 MHz; $CDCl_3$) 164.44 (C), 164.37 (C), 162.6 (C), 161.0 (C), 158.5 (C), 139.8 (C), 139.3 (C), 136.3 (C), 128.7 (CH), 128.1 (CH), 122.0 (CH), 121.4 (C), 118.6 (CH), 103.0 (C), 62.6 (CH_2), 47.5 (C), 24.8 (Me), 24.5 (Me), 14.0 (Me); *m*/*z* (CI) 367 (MH^+, 22), 314 (4), 297 (6), 279 (3), 257 (9), 218 (17), 192 (42), 168 (17), 140 (100).

Cycloadduct 14

Maleic anhydride cycloadduct **11** (248 mg, 0.64 mmol) was dissolved in acetonitrile (5 ml) and methanol (1 ml). The resulting mixture was heated at 50 °C for 3 h and then cooled to ~10 °C. Ethereal diazomethane (~0.4 mmol ml^{-1}; 3 ml) was added in one portion and the reaction mixture stirred to room temperature over 0.5 h and then heated to 50 °C for 0.1 h. The solvents were removed *in vacuo* and the resulting solid purified by chromatography on silica eluting with light petroleum–ethyl acetate (9 : 1) to give the *title compound* (126 mg, 45%) as colourless needles, mp 159–161 °C (from ethyl acetate–light petroleum); (Found: C, 57.9; H, 5.3; N, 3.0. $C_{21}H_{23}NO_7S$ requires C, 58.2; H, 5.4; N, 3.2%); (Found: MH^+, 434.1274. $C_{21}H_{23}NO_7S$ + H requires 434.1273); ν_{max} (KBr)/cm^{-1} 3074. 3004, 2972, 2949, 1747 (br), 1718, 1483, 1367, 1298, 1286, 1217, 1102, 767; δ_H (400 MHz; $CDCl_3$) 7.52 (1 H, dd, *J* 7.5, 1.0), 7.24 (1 H, m), 7.17–7.12 (2 H, m), 4.33 (2 H, q, *J* 7.1), 4.17 (1 H, d, *J* 9.3), 3.99 (1 H, d, *J* 9.3), 3.75 (3 H, s). 3.72 (3 H, s), 1.61 (3 H, s), 1.33 (3 H, s), 1.30 (3 H, t, *J* 7.1); δ_C (100 MHz; $CDCl_3$) 170.1 (C), 169.5 (C), 169.2 (C), 164.7 (C), 139.8 (C), 137.2 (C), 128.3 (CH), 124.8 (CH), 122.5 (CH), 113.8 (CH), 92.1 (C), 70.6 (C), 62.7 (CH_2), 56.1 (CH), 53.4 (Me), 52.7 (Me), 51.7 (CH), 44.5 (C) 26.7 (Me), 26.1 (Me), 14.0 (Me); *m*/*z* (CI) 451 (M + NH_4, 8%), 434 (MH^+, 46), 402 (52), 370 (27), 344 (50), 330 (16), 314 (9), 298 (17), 284 (26), 270 (39), 258 (21), 218 (100), 146 (50).

But-3-enyl diazoacetate 15

To dry dichloromethane (30 ml) was added glyoxylyl chloride tosylhydrazone[27] (4.56 g, 17.5 mmol) and 3-buten-1-ol (1.94 g, 26.3 mmol). *N*,*N*-Dimethylaniline (2.54 g, 21 mmol) was added dropwise and the resulting mixture stirred at room temperature for 1 h. Triethylamine (6.43 ml, 87.5 mmol) was added and the mixture stirred for 0.5 h before being poured into water (40 ml). The resulting mixture was extracted with ether (3 × 40 ml), ether extracts combined and washed with saturated brine (2 × 100 ml), and dried further over Na_2SO_4. Removal of the solvent *in vacuo* gave a yellow oil, which was purified further by chromatography on silica eluting with hexane–ether (9 : 1) to give the *title compound* (1.61 g, 66%) as a yellow oil. The title compound could be purified by short path distillation, bp 68–71 °C/0.5 mmHg (lit.,[22] bp not given); ν_{max} (film)/cm^{-1} 3084, 2981, 2960, 2900, 2112, 1701, 1653, 1394, 1355, 1247, 1188, 1051; δ_H (300 MHz; $CDCl_3$) 5.84–5.68 (1 H, m), 5.14–5.05 (2 H, m), 4.73 (1 H, s), 4.20 (2 H, t, *J* 6.7), 2.39 (2 H, m); δ_C (75.5 MHz; $CDCl_3$) 166.8 (C), 133.7 (CH), 117.3 (CH_2), 63.7 (CH_2), 46.2 (CH), 33.2 (CH_2).

But-3-enyl diazomalonyl chloride 16

To dry toluene (5 ml) under nitrogen was added triphosgene (1.04 g, 3.4 mmol) and the resulting solution cooled to −5 °C. Anhydrous pyridine (35 μl) was added and the mixture stirred to 0 °C over 2–3 min. But-3-enyl diazoacetate **15** (1.20 g, 8.6 mmol) was then added at such a rate that the internal temperature remained lower than 5 °C. After complete addition the mixture was stirred at room temperature for 5 h before being filtered through Celite and evaporated *in vacuo* to give a deep red oil. The crude product was purified by short path distillation to give two fractions, (i) bp 105–110 °C/0.4 mmHg, (ii) bp 130–138 °C/0.4 mmHg. The former proved to be 3-butenyl chloroacetate and the latter the *title compound* (248 mg, 14%) as a pale yellow oil, used without further purification, ν_{max} (film)/cm^{-1} 3082, 2983, 2966, 2908, 2154, 1778, 1707, 1643, 1385, 1309, 1236, 1165, 964; δ_H (300 MHz; $CDCl_3$) 5.86–5.71 (1 H, m), 5.21–5.06 (2 H, m), 4.36 (2 H, t, *J* 6.8), 2.46 (2 H, m); δ_C (75.5 MHz; $CDCl_3$) 158.4 (C), 153.5 (C), 133.0 (CH), 118.0 (CH_2), 65.4 (CH_2), 32.9 (CH_2); diazo not carbon observed.

Diazothioamide 17

A solution of but-3-enyl diazomalonyl chloride **16** (185 mg, 0.91 mmol) in dry ether (2 ml) was cooled to 0 °C on ice. In a separate flask 3,3-dimethyl-1,3-dihydroindole-2-thione **7** (147 mg, 0.83 mmol) in dry ether (8 ml) was cooled to 0 °C on

ice and treated with sodium hydride (60%, 34.7 mg, 0.87 mmol), stirred at 0 °C for 0.1 h and added dropwise to the acid chloride solution. The reaction mixture was stirred to room temperature for 1 h and poured into saturated brine (15 ml). The organic layer was separated, dried further over Na_2SO_4, filtered and the solvent removed *in vacuo*. The resulting yellow gum was purified by chromatography on silica eluting with light petroleum–dichloromethane (7 : 3) to give the *title compound* (90 mg, 32%) as a pale yellow oil; (Found: MH^+, 344.1073. $C_{17}H_{17}N_3O_3S$ + H requires 344.1069); ν_{max} (film)/cm^{-1} 3078, 2972, 2927, 2862, 2141, 1734, 1676 (br), 1458, 1352, 1299, 1236, 1136, 1036, 752; δ_H (300 MHz; $CDCl_3$) 7.33–7.17 (4 H, m), 5.78–5.60 (1 H, m), 5.12–5.06 (2 H, m), 4.22 (2 H, t, *J* 6.6), 2.41–2.34 (2 H, m), 1.50 (6 H, s); δ_C (75.5 MHz; $CDCl_3$) 214.0 (C), 163.4 (C), 158.8 (C), 140.7 (C), 139.2 (C), 133.1 (CH), 127.9 (CH), 125.0 (CH), 123.2 (CH), 117.2 (CH_2), 111.2 (CH), 64.8 (CH_2), 56.1 (C), 33.0 (CH_2), 28.5 (Me); diazo carbon not observed; *m*/*z* (CI) 361 (M + NH_4, 4%), 344 (MH^+, 3), 316 (28), 179 (7), 178 (45), 163 (9), 148 (37), 146 (100).

Thioisomünchnone 18

To a solution of dry toluene (1 ml) and dirhodium(II) tetraacetate (0.4 mg) under nitrogen at vigorous reflux was added diazothioamide **17** (65.0 mg, 0.19 mmol) in dry toluene (3 ml). After complete addition the reaction mixture was heated at reflux for a further 24 h. After this time the cooled reaction mixture was filtered, evaporated and the residue purified by chromatography on silica eluting with ethyl acetate to give the *title compound* (26 mg, 43%) as yellow prisms, mp 181–182 °C (from ethyl acetate); (Found: C, 64.1; H, 5.3; N, 4.3. $C_{17}H_{17}NO_3S$ requires C, 64.7; H, 5.4; N, 4.4%); (Found: MH^+, 316.1007. $C_{17}H_{17}NO_3S$ + H requires 316.1007); ν_{max} (KBr)/cm^{-1} 3072, 3043, 2994, 2969, 2911, 1716, 1637, 1464, 1431, 1396, 1345, 1155, 1130, 1115, 1074, 1005, 775, 756; δ_H (400 MHz; $CDCl_3$) 8.39 (1 H, d, *J* 7.8), 7.47–7.40 (3 H, m), 5.90–5.83 (1 H, m), 5.18–5.06 (2 H, m), 4.32 (2 H, t, *J* 6.9), 2.53–2.47 (2 H, m), 1.64 (6 H, s); δ_C (100 MHz; $CDCl_3$) 173.3 (C), 163.0 (C), 157.3 (C), 142.9 (C), 138.2 (C), 134.2 (CH), 129.1 (CH), 127.9 (CH), 122.6 (CH), 117.1 (CH_2), 115.7 (CH), 90.9 (C), 63.4 (CH_2), 49.0 (C), 33.4 (CH_2), 27.0 (Me); *m*/*z* (CI) 316 (MH^+, 20%), 237 (2), 197 (1), 190 (<1), 179 (8), 178 (14), 148 (36), 146 (100).

Cycloadduct 20

3,3-Dimethyl-1,3-dihydroindole-2-thione **7** (182.5 mg, 1.03 mmol) was dissolved in dry toluene (10 ml) under nitrogen. α-Bromoacetyl chloride (92 µl, 1.05 mmol) was added and the mixture stirred at room temperature for 0.1 h and at 60 °C for 1 h. After this time the mixture was cooled to room temperature and *N*-methylmaleimide (119 mg, 1.05 mmol) was added followed by the dropwise addition of triethylamine (307 µl, 2.16 mmol). After complete addition the mixture was heated at reflux for 3 h, cooled, filtered through Celite and evaporated *in vacuo*. The resulting red oil was purified by chromatography on silica eluting with light petroleum–ethyl acetate (9 : 1) to give the *title compound* (220 mg, 65%) as colourless prisms, mp 188–189 °C (from ethyl acetate–light petroleum); (Found: C, 62.2; H, 4.7; N, 8.4. $C_{17}H_{16}N_2O_3S$ requires C, 62.2; H, 4.9; N, 8.5%); (Found: MH^+, 329.0955. $C_{17}H_{16}N_2O_3S$ + H requires 329.0960); ν_{max} (KBr)/cm^{-1} 3010, 2999, 2978, 2962, 2951, 1774, 1734, 1699, 1479, 1458, 1387, 1340, 1306, 1288, 1120, 761; δ_H (400 MHz; $CDCl_3$) 7.55 (1 H, dd, *J* 8.0, 1.1), 7.26–7.22 (2 H, m), 7.16–7.12 (1 H, ddd, *J* 8.0, 7.5, 1.1), 4.35 (1 H, d, *J* 1.2), 3.86 (1 H, d, *J* 6.7), 3.79 (1 H, dd, *J* 6.7, 1.2), 3.08 (3 H, s), 1.74 (3 H, s), 1.56 (3 H, s); δ_C (100 MHz; $CDCl_3$) 173.8 (C), 173.5 (C), 173.2 (C), 139.5 (C), 138.5 (C), 128.1 (CH), 124.6 (CH), 122.1 (CH), 114.0 (CH), 95.8 (C), 56.6 (CH), 52.5 (CH), 46.5 (CH), 44.1 (C), 28.7 (Me), 25.5 (Me), 23.2 (Me); *m*/*z* (CI) 346 (M + NH_4, 100%), 329 (MH^+, 71), 312 (39), 295 (58), 283 (14), 212 (17), 146 (13).

Cycloadduct 21

3,3-Dimethyl-1,3-dihydroindole-2-thione **7** (549 mg, 1.03 mmol) was dissolved in dry toluene (10 ml) under nitrogen. α-Bromoacetyl chloride (272 µl, 3.10 mmol) was added and the mixture stirred at room temperature for 0.1 h and at 60 °C for 1 h. After this time the mixture was cooled to room temperature and dimethyl maleate (404 µl, 3.10 mmol) was added followed by the dropwise addition of triethylamine (926 µl, 6.51 mmol). After complete addition the mixture was heated at reflux overnight, cooled, filtered through Celite and evaporated *in vacuo*. The resulting red oil was purified by chromatography on silica eluting with light petroleum–ethyl acetate (85 : 15) to give the *title compound* (394 mg, 35%) as pale brown needles; mp 167–168 °C (from ethyl acetate–light petroleum); (Found: C, 59.8; H, 5.2; N, 3.8. $C_{18}H_{19}NO_5S$ requires C, 59.8; H, 5.3; N, 3.9%); (Found: MH^+, 362.1059. $C_{18}H_{19}NO_5S$ + H requires 362.1062); ν_{max} (KBr)/cm^{-1} 3037, 2966, 2950, 2889, 2850, 1732, 1709, 1593, 1491, 1375, 1321, 1244, 1227, 1167, 1054, 769; δ_H (400 MHz; $CDCl_3$) 7.51 (1 H, d, *J* 7.6), 7.22 (1 H, dd, *J* 7.9, 7.6), 7.16 (1 H, d, *J* 7.4), 7.10 (1 H, dd, *J* 7.9, 7.4), 4.28 (1 H, s), 3.92 (1 H, dd, *J* 9.0, 0.7), 3.87 (1 H, d, *J* 9.0), 3.77 (3 H, s), 3.74 (3 H, s), 1.60 (3 H, s), 1.37 (3 H, s); δ_C (100 MHz; $CDCl_3$) 172.9 (C), 170.7 (C), 169.3 (C), 139.9 (C), 137.4 (C), 128.1 (CH), 124.4 (CH), 122.4 (CH), 113.6 (CH), 95.7 (C), 56.0 (CH), 54.3 (CH), 52.8 (Me), 52.3 (Me), 49.8 (CH), 44.2 (CH), 27.0 (Me), 26.1 (Me); *m*/*z* (CI) 379 (M + NH_4, 100%), 362 (MH^+, 51), 347 (28), 332 (28), 330 (26), 270 (55), 218 (39), 180 (22).

The authors have deposited atomic coordinates with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. †

Acknowledgements

We thank the EPSRC for a studentship (to D. W.), the EPSRC Mass Spectrometry Centre at Swansea for mass spectra, and the EPSRC Chemical Database Service at Daresbury.[28]

† CCDC reference numbers 211109–211111. See http://www.rsc.org/suppdata/ob/b3/b305698h/ for crystallographic data in .cif or other electronic format.

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