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N-Acyl-2-methylaziridines: Synthesis and Utility in the C-Acylation of β-Ketoester Derived Dianions.

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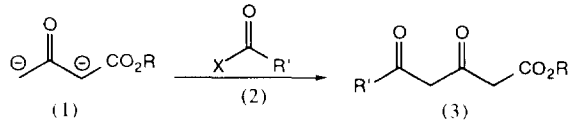
Dedicated to Emeritus Professor Hans Suschitzky on the occasion of his 80th birthday

Abstract: A "one pot" method for the preparation of N-acyl-2-methylaziridines is described, and the utility of these compounds in the C-acylation of dianions derived from β-ketoesters investigated. Application of this methodology to the synthesis of the polyketide natural product yangonin is also described.

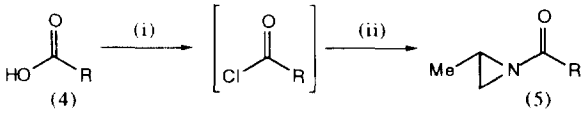
The C-acylation of β-ketoester derived dianions (1) is an important transformation in the context of polyketide synthesis, and is a process that has received significant attention in recent years (scheme 1). Despite this, the reaction of such dianions with the majority of acylating agents often leads to substantial amounts of O-acylation. Even systems that give good selectivity for C-acylation tend to give poor yields in the case of α,β-unsaturated acyl systems[1], as a consequence of competing Michael addition-type processes. To date only C-acylating agents based on the N-methoxy-N-methyl amide system (2, X = N(OMe)Me) appear to offer a general means of achieving this transformation[2]. In this paper we report full details of an alternative class of reagents, N-acyl-2-methylaziridines, which appear to be highly effective in the C-acylation of β-ketoester derived dianions, giving good yields with a wide range of acyl groups, including α,β-unsaturated systems[3].



(1) (2) (3)

Scheme 1

N-Acyl-2-methylaziridines can be readily prepared *via* the acylation of the parent 2-methylaziridine with an appropriate acid chloride in the presence of base[4,5]. However since the isolation and purification of acid chlorides is often problematic due to their moisture sensitivity, we decided to investigate the possibility of a "one pot" approach towards the acylaziridine systems starting from carboxylic acids, which hopefully would allow straightforward access to these systems.

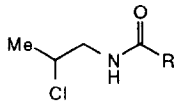


(4) (5)

Reagents: (i) $(COCl)_2$, rt, overnight; (ii) 2-methylaziridine, Et_3N, petroleum ether and/or dichloromethane

Scheme 2

It was found that this could be readily achieved by stirring the carboxylic acid with oxallyl chloride overnight, then removing the volatile components *in vacuo*, and adding an appropriate solvent, followed by triethylamine and the aziridine at 0°C (scheme 2). In general the preferred solvent for the reaction was petroleum ether since this resulted in almost complete precipitation of the triethylamine hydrochloride by-product during the reaction. This not only allowed the hydrochloride salt to be readily removed *via* simple filtration, but also minimised the formation of by-products (6) and (7) generated by the ring-opening of the acylaziridine with chloride ion. In addition, it was found that temperature control in this reaction was important, if the reaction system was allowed to warm substantially (>10°C), then significant amounts of the corresponding N-allyl amide (8) were also obtained.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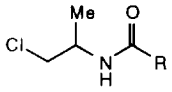
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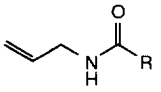
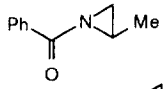
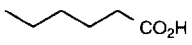
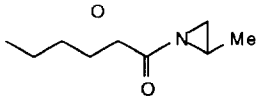
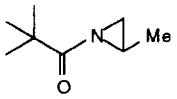
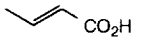
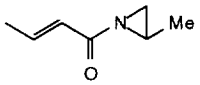
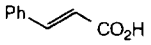
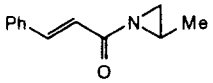
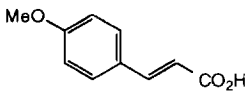
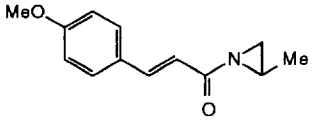
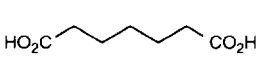
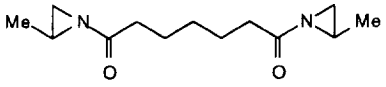

(8)

In some cases the acid chlorides used were not soluble in petroleum ether and consequently the reaction with 2-methylaziridine was slow, in these instances it was advantageous to use dichloromethane as a co-solvent in order to achieve reasonable reaction rates, however it is preferable to keep the dichloromethane to a minimum to avoid by-product formation as discussed above. Under these conditions we were able to prepare a range of N-acyl-2-methylaziridines in good overall yield (Table 1).

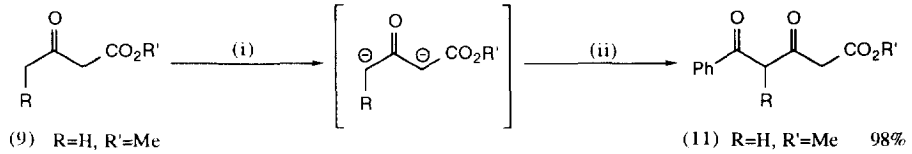
Table 1: *"One pot" formation of N-acyl-2-methylaziridines from carboxylic acids*

Entry	Acid	Product (5)	Overall Yield
a	$PhCO_2H$		86%
b			92%
c	$t\text{-}BuCO_2H$		87%
d			75%
e			76%
f			75%
g			64%

The N-acylaziridine products are stable to long term storage (> 1 year) at -20°C, and can be purified by either distillation or chromatography on silica gel, although they are usually obtained in sufficiently pure form

for direct use in subsequent acylation reactions. They are however readily degraded by strong acid (e.g. 3M hydrochloric acid), giving ring-opened products, and are also sensitive to high temperatures (>150°C), which leads to the formation of N-allyl amides (8).

With the N-acyl-2-methylaziridines in hand, we next examined the C-acylation process. It was the observation that the dianion derived from methyl acetoacetate (9) underwent clean C-acylation on reaction with N-benzoylaziridine (5a), that initially prompted us to undertake this investigation[6]. In this reaction we could find no evidence of O-acylation, or of reaction at C-2 of the β-ketoester[7]. In order to further probe this preference for C-acylation we examined the reaction using the γ-substituted β-ketoester (10), and again clean C-acylation was obtained in excellent yield (scheme 3).



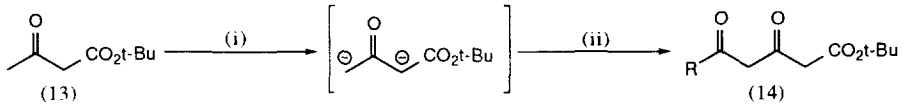
(9) R=H, R'=Me
(10) R=Me, R'=Et

(11) R=H, R'=Me 98%
(12) R=Me, R'=Et 100%

Reagents: (i) NaH, THF, rt; nBuLi, 0°C; (ii) (5a), 0°C.

Scheme 3.

Given the success of these initial reactions we examined the reaction between the dianion derived from *tert*-butyl acetoacetate and the range of N-acyl-2-methylaziridines prepared earlier (scheme 4).



(13) (14)

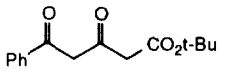
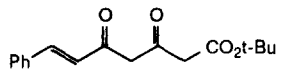
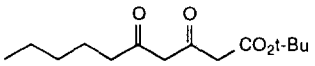
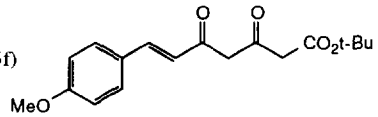
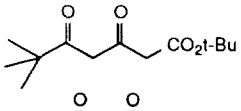
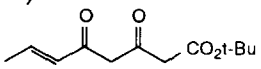
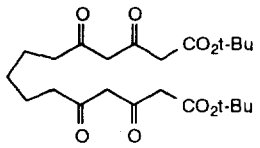
Reagents: (i) NaH, THF, rt; nBuLi, 0°C; (ii) (5a)-(5g), 0°C.

Scheme 4

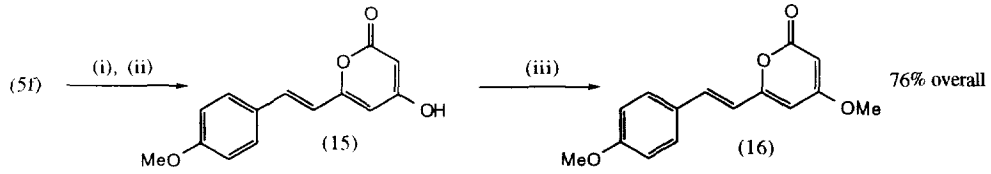
As can be seen from the results in table 2, excellent yields of the C-acylated products were obtained in the case of alkyl- and aryl-substituted N-acylaziridines (5a)-(5c), (5g), and good yields were even obtained with the relatively problematic α,β-unsaturated acylaziridines (5d)-(5f). In this sense the N-acyl-2-methylaziridines appear to be superior to previously reported reagents. In all cases the reactions were complete after 1-2h at 0°C, and were performed using stochiometric amounts of acylaziridine.

With the exception of products (12) and (14f), the resulting β,δ-diketoesters (14) all existed predominantly in a single mono-enol form (≥90%) in deuteriochloroform solution, with small amounts of the corresponding keto-form also present . Compound (14f) appears to exist in solution as a mixture of two mono-enol forms (one major), and the keto-form, and consequently produces a relatively complex ^{1}H nmr spectrum. This is presumably a consequence of the electron-donating *p*-methoxystyryl substituent stabilising the second enol form. Compound (12) is somewhat different in that it exists predominantly in the keto-form as a consequence of the γ-substituent which destabilises (allylic strain) the corresponding mono-enol.

Table 2: *Reaction between the dianion derived from tert-butyl acetoacetate (13) and N-acyl-2-methylaziridines (5a)-(5g).*

Aziridine	Product (14)	Yield	Aziridine	Product (14)	Yield
(5a)		96%	(5e)		58%
(5b)		98%	(5f)		53%
(5c)		93%			
(5d)		60%	(5g)		78%

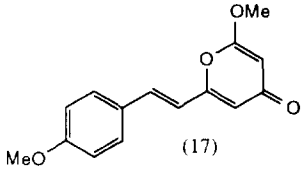
In order to examine the utility of these β,δ-diketoester systems as useful precursors to polyketide natural products, we investigated the conversion of intermediate (14f) into the pyrone natural product yangonin (16)[8] (scheme 5). This was readily achieved in very good overall yield by initial acid cleavage of the *tert*-butyl ester to give the corresponding carboxylic acid. Because we were somewhat concerned about the susceptibility of this carboxylic acid intermediate towards decarboxylation, we investigated a number of methods for its direct conversion into the desired pyrone system. It was found that this could most effectively be achieved by treating the crude carboxylic acid with acetic anhydride overnight. Evaporation of the acetic anhydride then gave the rather insoluble 4-hydroxypyrone intermediate (15), which was selectively methylated in the 4-position using methyl iodide in the presence of potassium carbonate, to give the natural product yangonin (16).



Reagents: (i) TFA, CH_2Cl_2, rt; (ii) Ac_2O, rt; (iii) K_2CO_3, MeI, DMF, rt.

Scheme 5

The melting point (154-155°C) and infra-red spectrum (vmax 1730cm^{-1}) were in accord with those previously reported for the natural product (155-157°C, vmax 1724cm^{-1})[8] On this point, it is worth noting that although the final methylation step could in principle give the alternative 2-methoxy isomer (17), this can easily be distinguised by infra-red spectroscopy (vmax 1667cm^{-1}), and none could be detected. Consequently this methylation procedure appears to be highly selective for the desired pyrone system.



Experimental:

Melting point determinations were carried out on an electrothermal apparatus and were recorded uncorrected. Infra-red absorption spectra were run neat on a Pye Unicam SP3-100 IR spectrophotometer. ^{1}H nmr spectra were recorded at 300MHz on a Bruker AC-300 instrument, as solutions in deuteriochloroform. Chemical shifts are referenced to tetramethylsilane, and J-values are rounded to the nearest 0.5Hz. Mass spectra were recorded using ammonia chemical ionisation at low resolution on a Finnigan 4500 instrument, and at high resolution on a Kratos Concept 1-S instrument. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} glass-backed plates. The plates were visualised by the use of a UV lamp, or by dipping in a solution of vanillin in ethanolic sulfuric acid, followed by heating. Silica gel particle sizes 40-63μm was employed for flash chromatography. All solvents were dried using standard procedures.[9]

General Procedure for N-Acylation of 2-methylaziridine. The carboxylic acid (10.0mmol) was treated with oxalyl chloride (5ml) and the mixture stirred at room temperature for 18h under argon. The volatile components were then removed in vacuo, and the residue dissolved in dry petroleum ether (50ml). This solution was then cooled to 0°C and treated sequentially with triethylamine (11.0mmol) and 2-methyl aziridine (10.0mmol). The mixture was stirred at 0°C for 30min., then diluted with diethyl ether (50ml) and filtered through a pad of Celite. The solvents were then removed under reduced pressure to give the crude product.

Preparation of N-Benzoyl-2-methylaziridine (5a). Benzoic acid (760mg, 6.24mmol) was treated with oxallyl chloride (3ml), followed by triethylamine (960μl, 6.85mmol) and 2-methylaziridine (440μl, 6.24mmol), according to the general procedure outlined above. The resulting residue was then purified by chromatography on silica gel (20% ethyl acetate - 80% petroleum ether) to give N-benzoyl-2-methylaziridine (950mg, 86%) as a colourless oil. Rf: 0.7 (50% ethyl acetate - 50% petroleum ether). This material gave ^{1}H and IR data in accord with that previously reported[5].

Preparation of N-Hexanoyl-2-methylaziridine (5b). Hexanoic acid (720mg, 6.24mmol) was treated with oxallyl chloride (3ml), triethylamine (960μl, 6.85mmol) and 2-methyl aziridine (440μl, 6.24mmol), according to the general procedure outlined above. The resulting residue was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give N-hexanoyl-2-methylaziridine (890mg, 92%) as a colourless oil. Rf: 0.5 (25% ethyl acetate - 75% petroleum ether).
νmax: 1685cm^{-1}; ^{1}H nmr: δ 2.49-2.41(1H, m, *H*-2), 2.36(2H, t, J=7.5Hz, C*H*$_2$-2'), 2.30(1H, d, J=6.0Hz, H_a-3), 1.90(1H, d, J=3.5Hz, H_b-3), 1.75-1.58(4H, m), 1.38-1.21(2H, m), 1.29(3H, d, J=5.0Hz, C*H*$_3$), 0.78(3H, t, J=6.5Hz, C*H*$_3$); m/z: 173(M+NH$_4^+$, 100%), 156(M+H$^+$, 31%). Found [M+NH$_4$]$^+$ 173.1645 $C_9H_{21}N_2O$ requires 173.1654

Preparation of N-Pivaloyl-2-methylaziridine (5c). Pivalic acid (636mg, 6.24mmol) was treated with oxallyl chloride (3ml), triethylamine (960μl, 6.85mmol) and 2-methyl aziridine (440μl, 6.24mmol), according to the general procedure outlined above. The resulting residue was purified by chromatography on silica gel (15% ethyl acetate - 85% petroleum ether) to give N-pivaloyl-2-methylaziridine (765mg, 87%) as a colourless oil. Rf: 0.25 (25% ethyl acetate - 75% petroleum ether).

vmax: 1660cm^{-1}; ^{1}H nmr: δ 2.44-2.37(2H, m, *H*-2, H_a-3), 1.83(1H, d, J=3.5Hz, H_b-3), 1.31(3H, d, J=5.0Hz, CH_3), 1.22(9H, s, $COC(CH_3)_3$); m/z: 159($M+NH_4^+$, 62%), 142($M+H^+$, 100%). Found $[M+H]^+$ 142.1226 $C_8H_{16}NO$ requires 142.1232

Preparation of (*E*)-N-Crotonoyl-2-methylaziridine (5d). (*E*)-Crotonic acid (537mg, 6.24mmol) was treated with oxallyl chloride (3ml), followed by triethylamine (960µl, 6.85mmol) and 2-methyl aziridine (440µl, 6.24mmol), according to the general procedure outlined above. The resulting residue was purified by chromatography on silica gel (20% ethyl acetate - 80% petroleum ether) to give (*E*)-N-crotonoyl-2-methylaziridine[4] (585mg, 75%) as a colourless oil. Rf: 0.55 (50% ethyl acetate - 50% petroleum ether).
vmax: 1675, 1635cm^{-1}; ^{1}H nmr: δ 6.93(1H, dq, J=15.5, 7.0Hz, *H*-3'), 6.01(1H, dq, J=15.5, 1.5Hz, *H*-2'), 2.48-2.39(1H, m, *H*-2), 2.34(1H, d, J=6.0Hz, H_a-3), 1.95(1H, d, J=3.5Hz, H_b-3), 1.87(3H, dd, J=7.0, 1.5Hz, CH_3-4'), 1.31(3H, J=6.5Hz, CH_3); m/z: 126($M+H^+$, 100%), 69(80%). Found $[M+H]^+$ 126.0921 $C_7H_{12}NO$ requires 126.0919

Preparation of (*E*)-N-Cinnamoyl-2-methylaziridine (5e). (*E*)-Cinnamic acid (720mg, 6.24mmol) was treated with oxallyl chloride (3ml), triethylamine (960µl, 6.85mmol) and 2-methyl aziridine (440µl, 6.24mmol), according to the general procedure outlined above. The resulting residue was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give (*E*)-N-cinnamoyl-2-methylaziridine (887mg, 76%) as a colourless oil. Rf: 0.65 (50% ethyl acetate - 50% petroleum ether).
vmax: 1670, 1626 cm^{-1}; ^{1}H nmr: δ 7.68(1H, d, J=16.0Hz, *H*-3'), 7.61-7.42(2H, m, *o*-Ar*H*), 7.38-7.36(3H, m, Ar*H*), 6.62(1H, d, J=16.0Hz, *H*-2'), 2.62-2.53(1H, m, *H*-2), 2.44(1H, d, J=6.0Hz, H_a-3), 2.06(1H, d, J=3.5Hz, H_b-3), 1.38(3H, d, J=5.5Hz, CH_3); m/z: 205($M+NH_4^+$, 21%), 188($M+H^+$, 100%). Found $[M+NH_4]^+$ 205.1346 $C_{12}H_{17}N_2O$ requires 205.1341

Preparation of (*E*)-N-(*p*-Methoxycinnamoyl)-2-methylaziridine (5f). (*E*)-*p*-Methoxycinammic acid (2.78g, 15.6mmol) was treated with oxallyl chloride (7ml) and the mixture stirred at room temperature for 18h under argon. The volatile components were then removed in vacuo, and the residue dissolved in a mixture of dry petroleum ether (40ml) and dry dichloromethane (20ml). This solution was then cooled to 0°C and treated sequentially with triethylamine (2.4ml, 17.1mmol) and 2-methyl aziridine (1.1ml, 15.6mmol). The mixture was stirred at 0°C for 30min., then diluted with diethyl ether (40ml) and filtered through a pad of Celite. The solvents were then removed under reduced pressure and the residue purified by chromatography on silica gel (20% ethyl acetate - 80% petroleum ether) to give (*E*)-N-(*p*-methoxycinnamoyl)-2-methylaziridine (2.53g, 75%) as a colourless oil. Rf: 0.5 (50% ethyl acetate - 50% petroleum ether).
vmax: 1660, 1620cm^{-1}; ^{1}H nmr: δ 7.63(1H, d, J=16.0Hz, C*H*Ar), 7.47(2H, d, J=9.0Hz, *o*-Ar*H*), 6.89(2H, d, J=9.0Hz, *m*-Ar*H*), 6.49(1H, d, J=16.0Hz, C*H*CO), 3.28(3H, s, OCH_3), 2.59-2.50(1H, m, C*H*Me), 2.41(1H, d, J=6.0Hz, CH_aH_bN), 2.03(1H, d, J=4.0Hz, CH_aH_bN), 1.37(3H, d, J=6.5Hz, CH_3); m/z: 218($M+H^+$, 100%). Found $[M+H]^+$ 218.1180 $C_{13}H_{16}NO_2$ requires 218.1180

Preparation of Bis-(2-methylaziridinyl)hepta-1',7'-diamide (5g). Pimelic acid (1.0g, 6.24mmol) was treated with oxallyl chloride (3ml) and the mixture stirred at room temperature for 18h under argon. The volatile components were then removed in vacuo, and the residue dissolved in dry dichloromethane (20ml).

This solution was then cooled to 0°C and treated sequentially with triethylamine (1.92ml, 13.7mmol) and 2-methyl aziridine (0.88ml, 12.5mmol). The mixture was left at 0°C for 30min., then diluted with diethyl ether (20ml) and filtered through a pad of Celite. The solvents were then removed under reduced pressure and the residue purified by chromatography on silica gel (30% ethyl acetate - 70% petroleum ether) to give bis-(2-methylaziridinyl)hepta-1',7'-diamide (950mg, 64%) as a colourless oil. Rf: 0.2 (50% ethyl acetate - 50% petroleum ether).
vmax: 1675cm^{-1}; ^{1}H nmr: δ 2.48-2.41(2H, m, 2xC*H*Me), 2.37(4H, t, J=7.5Hz, 2 x COCH_2), 2.30(2H, d, J=6.0Hz, 2 x CH_aH$_b$N), 1.90(2H, d, J=3.5Hz, 2 x CH$_a$$H_b$N), 1.70-1.31(6H, m), 1.29(6H, d, J=5.5Hz, 2 x CH_3); m/z: 256(M+NH$_4^+$, 7%), 239(M+H$^+$, 32%), 69(100%). Found [M+H]$^+$ 239.1769 $C_{13}H_{23}N_2O_2$ requires 239.1759

General Procedure for the Reaction of β-Ketoester Derived Dianions With N-Acyl-2-methylaziridines. The β-ketoester (1.0mmol) was added dropwise to a stirred suspension of sodium hydride (44mg of a 60% suspension in oil, washed twice with petroleum ether, *ca.* 1.1mmol) in dry THF (5ml) under argon. The resulting mixture was stirred for a further 20min, then cooled to 0°C and n-butyl lithium (758μl of a 1.46M solution in hexanes, 1.1mmol) added dropwise. The resulting mixture was stirred at 0°C for 10min, then a solution of the N-acyl-2-methylaziridine (1.0mmol) in dry THF (1ml) added. The solution was stirred for a further 1-2h at 0°C, then 3M hydrochloric acid (20ml) added, and the mixture extracted with ethyl acetate (3x20ml). The extracts were washed with saturated aqueous sodium chloride (2x20ml), dried ($MgSO_4$), and the solvent removed under reduced pressure.

Preparation of Methyl 3,5-Dioxo-5-phenylpentanoate (11). The dianion derived from methyl 3-oxobutanoate (104μl, 0.97mmol) was reacted with N-benzoyl-2-methylaziridine (172mg, 0.97mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give methyl 3,5-dioxo-5-phenylpentanoate (210mg, 98%) as a colourless oil. Rf: 0.35 (20% ethyl acetate - 80% petroleum ether).
vmax: 3420, 1715cm^{-1}; ^{1}H nmr: δ enol form; 7.87-7.85(2H, *o*-Ar*H*), 7.52-7.43(3H, m, Ar*H*), 6.27(1H, br.s, *H*-4), 3.74(3H, s, CO2CH_3), 3.47(2H, s, CH_2-2); m/z: 238(M+NH$_4^+$, 100%), 221(M+H$^+$, 20%), 69(38%). Found [M+NH$_4$]$^+$ 238.1078 $C_{12}H_{16}NO_4$ requires 238.1079.

Preparation of Ethyl 3,5-Dioxo-4-methyl-5-phenylpentanoate (12). The dianion derived from ethyl 3-oxo-pentanoate (109μl, 0.97mmol) was reacted with N-benzoyl-2-methylaziridine (172mg, 0.97mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give ethyl 3,5-dioxo-4-methyl-5-phenylpentanoate (240mg, 100%) as a colourless oil. Rf: 0.4 (25% ethyl acetate - 75% petroleum ether).
vmax: 3410, 1715, 1662cm^{-1}; ^{1}H nmr: δ keto-form; 7.98(5H, m, Ar*H*), 4.73(1H, q, J=7.0Hz, *H*-4), 4.08(2H, q, J=7.0Hz, CO_2CH_2), 3.50(2H, s, CH_2-2), 1.43(3H, d, J=7.0Hz, CH_3), 1.16(3H, t, J=7.0Hz, CH_3); m/z: 266(M+NH$_4^+$, 100%), 249(M+H$^+$, 11%). Found [M+NH$_4$]$^+$ 266.1394 $C_{14}H_{20}NO_4$ requires 266.1392.

Preparation of *tert*-Butyl 3,5-Dioxo-5-phenylpentanoate (14a). The dianion derived from *tert*-butyl 3-oxobutanoate (161µl, 0.97mmol) was reacted with N-benzoyl-2-methylaziridine (5a) (131mg, 0.97mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (20% ethyl acetate - 80% petroleum ether) and then recrystallised from petroleum ether at -20°C to give *tert*-butyl 3,5-dioxo-5-phenylpentanoate (244mg, 96%) as a white crystalline soid, mp 65-66°C. Rf: 0.5 (20% ethyl acetate - 80% petroleum ether).
vmax: 3410, 1724cm^{-1}; ^{1}H nmr: δ enol form; 7.87-7.84(2H, *o*-Ar*H*), 7.52-7.41(3H, m, Ar*H*), 6.27(1H, s, *H*-4), 3.37(2H, s, CH_2-2), 1.47(9H, $CO_2C(CH_3)_3$); m/z: 280(M+NH_4^+, 100%), 263(M+H^+, 58%), 224(35%), 218(35%), 215(24%), 162(25%). Found $[M+H]^+$ 263.1285 $C_{15}H_{19}O_4$ requires 263.1283

Preparation of *tert*-Butyl 3,5-Dioxodecanoate (14b). The dianion derived from *tert*-butyl 3-oxobutanoate (96µl, 0.58mmol) was reacted with N-hexanoyl-2-methylaziridine (5b) (90mg, 0.58mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (5% ethyl acetate - 95% petroleum ether) to give *tert*-butyl 3,5-dioxodecanoate (146mg, 96%) as a pale yellow oil. Rf: 0.7 (20% ethyl acetate - 80% petroleum ether).
vmax: 3415, 1738, 1615cm^{-1}; ^{1}H nmr: δ enol form; 5.57(1H, s, *H*-4), 3.23(2H, s, CH_2-2), 2.27(2H, t, J=7.5Hz, CH_2-6), 1.63-1.52(2H, m, CH_2-7), 1.45(9H, s, $C(CH_3)_3$), 1.36-1.23(4H, m, CH_2-8, CH_2-9), 0.89-0.84(3H, m, CH_3-10); m/z: 274(M+NH_4^+, 100%), 257(M+H^+, 44%), 218(65%), 201(30%). Found $[M+H]^+$ 257.1755 $C_{14}H_{25}O_2$ requires 257.1753.

Preparation of *tert*-Butyl 6,6-Dimethyl-3,5-dioxoheptanoate (14c). The dianion derived from *tert*-butyl 3-oxobutanoate (129µl, 0.78mmol) was reacted with N-pivolyl-2-methylaziridine (5c) (110mg, 0.78mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (5% ethyl acetate - 95% petroleum ether) to give *tert*-butyl 6,6-dimethyl-3,5-dioxoheptanoate (176mg, 93%) as a colourless oil. Rf: 0.75 (25% ethyl acetate - 75% petroleum ether).
vmax: 3410, 1736, 1605cm^{-1}; ^{1}H nmr: δ enol form; 5.68(1H, s, *H*-4), 3.25(2H, s, CH_2-2), 1.45(9H, s, $CO_2C(CH_3)_3$), 1.15(9H, s, $COC(CH_3)_3$); m/z: 260(M+NH_4^+, 100%), 243(M+H^+, 62%), 187(66%), 176(31%), 159(52%), 142(73%). Found $[M+H]^+$ 243.1590 $C_{13}H_{23}O_4$ requires 243.1596

Preparation of (*E*)-*tert*-Butyl 3,5-Dioxo-oct-6-enoate (14d). The dianion derived from *tert*-butyl 3-oxobutanoate (128µl, 0.77mmol) was reacted with (*E*)-N-crotonoyl-2-methylaziridine (5d) (96mg, 0.77mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give (*E*)-*tert*-butyl 3,5-dioxo-oct-6-enoate[2] (105mg, 60%) as a colourless oil. Rf: 0.5 (25% ethyl acetate - 75% petroleum ether)
vmax: 3470, 1738, 1650cm^{-1}; ^{1}H nmr: δ enol form; 6.92-6.80(1H, m, *H*-7), 5.85(1H, br.d, J=15.5Hz, *H*-6), 5.54(1H, s, *H*-4), 3.28(2H, s, CH_2-2), 1.89(3H, br.d, J=7.0Hz, CH_3-8), 1.45(9H, s, $C(CH_3)_3$); m/z: 244(M+NH_4^+, 100%), 227(M+H^+, 28%), 188(24%). Found $[M+H]^+$ 227.1276 $C_{12}H_{19}O_4$ requires 227.1283.

Preparation of (*E*)-*tert*-Butyl 3,5-Dioxo-7-phenylhept-6-enoate (14e). The dianion derived from *tert*-butyl 3-oxobutanoate (503µl, 3.04mmol) was reacted with (*E*)-N-cinnamoyl-2-methylaziridine (5e)

(569mg, 3.04mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (5% ethyl acetate - 95% petroleum ether) to give (*E*)-*tert*-butyl 3,5-dioxo-7-phenylhept-6-enoate[2] (508mg, 58%) as a pale yellow oil. Rf: 0.5 (25% ethyl acetate - 75% petroleum ether)

vmax: 3400, 1727, 1642cm^{-1}; ^{1}H nmr: δ enol form; 7.60(1H, d, J=16.0Hz, *H*-7), 7.52-7.49(2H, m, *o*-Ar*H*), 7.37-7.35(3H, m, Ar*H*), 6.46(1H, d, J=16.0Hz, *H*-6), 5.73(1H, s, *H*-4), 3.34(2H, s, C*H*$_2$-2), 1.46(9H, s, C(C*H*$_3$)$_3$); m/z: 289(M+H$^+$, 100%), 250(21%), 233(79%). Found [M+H]$^+$ 289.1435 $C_{17}H_{21}O_4$ requires 289.1440

Preparation of (*E*)-*tert*-Butyl 3,5-Dioxo-7-(*p*-methoxyphenyl)heptanoate (14f). The dianion derived from *tert*-butyl 3-oxobutanoate (511µl, 3.09mmol) was reacted with (*E*)-N-(*p*-methoxycinnamoyl)-2-methylaziridine (5f) (790mg, 3.09mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (10% ethyl acetate - 90% petroleum ether) to give (*E*)-*tert*-butyl 3,5-dioxo-7-(*p*-methoxyphenyl)heptanoate (521mg, 53%) as a pale yellow oil. Rf: 0.8 (50% ethyl acetate - 50% petroleum ether).

^{1}H nmr: δ major mono-enol form: 7.57(1H, d, J=15.5Hz, *H*-7), 7.46(2H, d, J=9.0Hz, *o*-Ar*H*), 6.89(2H, d, J=9.0Hz, *m*-Ar*H*), 6.33(1H, d, J=15.5Hz, *H*-6), 5.69(1H, s, enol-*H*), 3.82(3H, s, OC*H*$_3$), 3.32(2H, s, C*H*$_2$-), 1.46(9H, s, C(C*H*$_3$)$_3$); m/z: 319(M+H$^+$, 100%), 263(52%). Found [M+H]$^+$ 319.1540 $C_{18}H_{23}O_5$ requires 319.1545.

Preparation of Di-*tert*-butyl 3,5,11,13-Tetraoxopentadeca-1,15-dioate (14g). The dianion derived from *tert*-butyl 3-oxobutanoate (282µl, 1.7mmol) was reacted with bis-(2-methylaziridinyl)hepta-1',7'-diamide (5g) (200mg, 0.84mmol) according to the general procedure outlined above. The resulting crude product was purified by chromatography on silica gel (5% ethyl acetate - 95% petroleum ether) to give di-*tert*-butyl 3,5,11,13-tetraoxopentadeca-1,15-dioate (289mg, 78%) as a pale yellow oil. Rf: 0.4 (50% ethyl acetate - 50% petroleum ether).

vmax: 3461, 1728, 1612cm^{-1}; ^{1}H nmr: δ bis-enol form; 5.55(2H, s, *H*-4, *H*-12), 3.21(4H, s, C*H*$_2$-2, C*H*$_2$-14), 2.27(4H, t, J=7.5Hz, C*H*$_2$-6, C*H*$_2$-10), 1.65-1.29(6H, m), 1.44(18H, s, 2 x C(C*H*$_3$)$_3$); m/z: 458(M+NH$_4^+$, 41%), 376(82%), 359(50%), 332(79%), 320(80%), 302(44%), 245(62%), 228(100%). Found [M+NH$_4$]$^+$ 458.2757 $C_{23}H_{40}NO_8$ requires 458.2754

Preparation of Yangonin (16). Trifluoroacetic acid (2ml) was added dropwise to a stirred solution of *tert*-butyl 3,5-dioxo-7-(*p*-methoxyphenyl)heptanoate (250mg, 0.79mmol) in dry dichloromethane (5ml) at 0°C under argon. After the addition was complete the reaction mixture was allowed to warm to room temperature and stirred for 1h. The volatile reaction components were then removed in vacuo and the residue treated with acetic anhydride (5ml). The resulting solution was stirred at room temperature under argon for 18h, and then the volatile reaction components were again removed *in vacuo*. The residue was dissolved in dry DMF (5ml) containing potassium carbonate (200mg) and methyl iodide (1ml), and the mixture stirred at room temperature under argon for 18h. The reaction mixture was then poured into ethyl acetate (30ml) and 2M hydrochloric acid (20ml). The organic layer was washed with brine (20ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give an orange solid which was purified by chromatography on silica gel (50% ethyl

acetate - 50% petroleum ether) to give a bright yellow solid. The product was then recrystallised from ethyl acetate - petroleum ether to give yangonin (154mg, 76%), m.p. 154-155°C (lit. m.p. 155-157°C[8]). Rf: 0.6 (75% ethyl acetate - 25% petroleum ether).

vmax: 1730, 1645cm^{-1}; ^{1}H nmr: δ 7.44(1H, d, J=16.0Hz, C=C*H*Ar), 7.43(2H, d, J=8.5Hz, *o*-Ar*H*), 6.88(2H, d, J=8.5Hz, *m*-Ar*H*), 6.43(1H, d, J=16.0Hz, C*H*=CAr), 5.87(1H, d, J=2.0Hz), 5.45(1H, d, J=2.0Hz), 3.82(3H, s, OCH_3), 3.80(3H, s, OCH_3); m/z: 276(M+NH_4^+, 100%), 259(M+H^+, 49%). Found $[M+H]^+$ 259.0965 $C_{15}H_{15}O_4$ requires 259.0970.

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