Chemistry of Pseudomonic Acid. Part 16

Aryl and Heteroaryl Ketone Derivatives of Monic Acid

ANGELA ABSON, NIGEL J. P. BROOM, PHILIPPA A. COATES, JOHN S. ELDER, ANDREW K. FORREST*, PETER C. T. HANNAN, AMANDA J. HICKS, PETER J. O'HANLON, NICKY D. MASSON (née STEEL), NEIL D. PEARSON, JEAN E. PONS and JENNIFER M. WILSON

SmithKline Beecham Pharmaceuticals,
Brockham Park, Betchworth, Surrey, RH3 7AJ, U.K.

(Received for publication October 16, 1995)

The synthesis, antibacterial activities, murine pharmacokinetic and infection model data for a range of aryl and heteroaryl ketone derivatives of monic acid (**2a**) are reported. The best results were found for the 3-furyl and 2-methoxy thiazol-5-yl analogues.

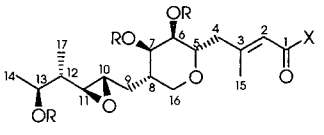
Pseudomonic acid A (**1a**) (mupirocin) is an antibiotic produced by *Pseudomonas fluorescens*[1]. It is marketed by SmithKline Beecham as the active component of the product Bactroban† ointment for the topical treatment of skin infections. On systemic administration of mupirocin to man, hydrolysis to antibacterially inactive monic acid (**2a**) occurs[2], precluding its use as a systemic agent. The syntheses of antibacterially active ester[3], alkyl ketone[4] and heterocyclic[5] derivatives of monic acid have been described.

We would like to disclose the results of our investigation into a range of aryl and heteroaryl ketone derivatives of monic acid.

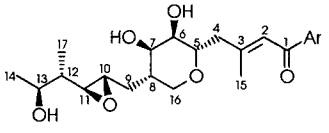
Chemistry

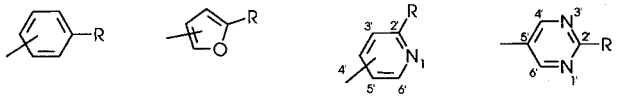
Previous approaches to monic acid ketone derivatives used either the anhydride (**3b**)[4] or aldehyde (**4b**)[4,6]. We found the reaction of monic acid Weinreb reagent[7] (**5b**) with organo-lithium or -cerium[8] reagents to be a convenient alternative. The Weinreb reagent (**5b**) could be prepared from monic acid as a crystalline solid in 80% yield without recourse to chromatography. As outlined below, the aldehyde (**4b**) was preferred for reaction with less stable anions, MnO_2 oxidation of the intermediate alcohol then yielding the ketone. Finally, trimethylsilyl (TMS) protection was removed by mild

Aryl- and heteroaryl lithiums were prepared by bromine-lithium exchange or by deprotonation[9] with *n*-butyllithium where appropriate. The sulfoxide (**8f**) was obtained by oxidising the sulfide (**8e**) with *m*-chloroperbenzoic acid in a two phase dichloromethane/sat-

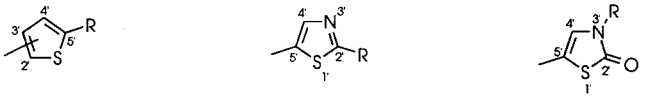


1 X = $O(CH_2)_3CO_2H$ **a**: R = H
2 X = OH **b**: R = $SiMe_3$
3 X = $OCO_2{}^tBu$
4 X = H
5 X = NMeOMe





6 o- **9** 2'-yl **11** 4'-yl **14**
7 m- **10** 3'-yl **12** 5'-yl
8 p- **13** 6'-yl



15 2'-yl **17** **18**
16 3'-yl

	R		R
a	H	g	COMe
b	OMe	h	CF_3
c	OH	i	
d	NMe_2	j	
e	SMe	k	Me
f	S(O)Me	l	^nPr

† Trademark of SmithKline Beecham.

urated aqueous sodium hydrogen carbonate medium, while other reactive or acidic functionality was introduced in protected form. Thus phenolic hydroxyls were protected by prior deprotonation with sodium hydride (in the case of **6c**), or with a triethylsilyl (TES) group (in the case of **8c**), before bromine-lithium exchange. The acetyl substituents of **8g** and **10g** were introduced as TMS and TES enol ethers[10] respectively.

The starting material for **10k** was prepared by an extension of a useful 3-halofuran synthesis[11].††

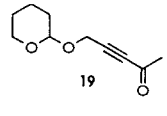
2-Substituted thiazoles could generally be directly deprotonated in the 5-position, thus starting thiazoles with oxygen, sulphur and nitrogen linked substituents smoothly yielded products **17b**, **17e**, **17d** and **17i**. However, the electronic nature of the 2-thiazolyl moiety resulted in side reactions when the synthesis of the other thiazole examples were attempted. Thus the TES enol ether proved too labile to be useful protection for 2-

Table 1. Synthetic methods, antibacterial activities and serum binding for monic ketones.

	Yield %	Method[a]	Polarity[b]	Antibacterial activity (MIC $\mu g/ml^{-1}$)*							Human serum binding[c] % bound
				Staphylococcus aureus NCTC 6571	*Staphylococcus aureus* Smith	*Streptococcus pyogenes* CN10	*Streptococcus pneumoniae* PU7	*Haemophilus influenzae* Q1	*Moraxella catarrhalis* 1502	*Staphylococcus hominis* BW	
1a	—	—	—	0.13	0.25	0.13	0.13	0.06	0.13	0.5	>95
6a		A	0.18	0.5	0.5	1	1	0.06	0.5	2	90
6b	67	A	0.15	1	1	8	4	1	0.13	16	—
6c	26	A	0.27	8	8	32	8	8	1	16	—
7b	39	A	0.24	0.5	0.25	8	2	—	0.5	4	—
8b	52	A	0.21	0.5	0.25	0.25	0.25	0.03	0.25	0.5	96
8c	30	A	−0.16	2	2	0.5	0.5	0.03	0.13	8	65
8d	45	A	0.35	0.25	0.25	0.13	0.13	0.25	0.25	2	97
8e	57	A	0.41	0.25	0.25	0.13	0.25	0.06	0.06	1	96
8f	65	see text	−0.18	2	2	0.5	1	0.06	0.25	4	56
8g	36	A	0.07	0.25	0.13	0.13	0.13	0.13	0.06	1	85
8h	57	A	0.56	0.5	0.5	0.25	0.13	0.5	0.13	2	90
9a	8	A	−0.14	0.25	1	1	1	0.06	0.06	2	—
10a	73	A	−0.07	0.25	0.25	1	0.5	0.06	0.13	1	56
10b	4	A	0.11	0.5	0.5	1	0.5	0.25	0.25	4	—
10g	7	A	−0.09	1	1	1	1	1	0.25	4	—
10k	58	A	0.11	0.25	0.5	0.5	0.25	0.06	0.13	2	95
11a	10	A	−0.04	0.5	0.5	0.5	0.5	0.06	0.13	4	48
12a	23	D	−0.03	0.5	0.5	1	1	—	0.5	4	49
12b	39	D	0.12	0.25	0.25	0.25	0.5	0.13	0.5	2	84
12d	38	D	0.18	0.25	0.25	0.25	0.25	0.13	0.13	2	92
12e	36	D	0.23	0.25	0.5	0.25	0.25	0.13	0.13	1	90
12i	50	B	—	0.5	0.5	0.13	0.06	0.5	0.06	1	—
13a	32	A	−0.05	1	1	2	2	0.25	—	4	—
14b	33	D	−0.07	0.25	0.5	0.5	0.25	0.13	1	2	67
14d	9	D	0.12	0.25	0.25	0.5	0.25	0.13	0.25	1	80
14i	38	D	0.49	0.13	9.13	0.13	0.25	0.5	0.25	1	86
14j	51	A	0.16	0.25	0.25	0.5	0.25	0.06	0.13	1	72
15a	27	A	0.09	0.25	0.13	0.5	0.25	0.06	0.13	1	85
15b	48	A	0.23	0.13	0.25	0.25	0.13	0.06	0.06	0.5	95
16a	84	A	−0.08	0.5	0.25	1	0.5	0.06	0.13	0.5	—
17a	25	C	−0.06	0.5	0.25	1	0.5	0.06	0.13	1	65
17b	42	A	0.03	0.25	0.13	0.25	0.25	0.06	0.06	0.5	87
17d	15	A	0.1	1	1	1	0.5	0.25	0.5	—	—
17e	51	A	0.15	0.13	0.25	—	0.13	0.06	0.13	0.5	91
17g	15	A	0.03	0.25	0.25	0.5	0.25	0.13	0.13	1	76
17i	14	A	0.4	0.5	0.25	0.5	—	—	0.25	1	93
17k	47	C	0.04	0.5	0.5	0.5	0.25	0.06	0.13	4	67
18k	34	A	−0.28	0.5	0.25	0.13	0.13	0.06	0.03	2	43
18l	31	A	−0.05	0.25	0.25	0.5	0.5	—	0.25	1	—

[a] A: Organolithium reagent reacting with Weinreb reagent **5b**. B: Organocerium reagent reacting with **5b**. C: Organolithium reagent reacting with aldehyde **4b**. D: Organocerium reagent reacting with **4b**. [b] Polarity was estimated using reverse phase tlc on Merck 5747 plates eluting with 1:1 methanol:0.1 M pH 7 phosphate buffer. The figure quoted is $\log_{10}$ (1/rf − 1) where rf is the measured retention factor. [c] By ultrafiltration (Amicon microfree partition apparatus) using sterile pooled human serum; initial compound concentration 40 $\mu g\,ml^{-1}$.

†† The protected keto alcohol (**19**) could be cleanly cyclised with hydrobromic acid to 4-bromo-2-methylfuran in 60% yield when furan was included as a carbonium ion trap.



19

Table 2. Pharmacokinetic and infection model data for selected monic ketones.

Compound	Mouse blood level 50 mg kg^{-1} AUC (μg ml^{-1} minute)		CD_{50}[a] (mg kg^{-1})	
	oral	s.c.	oral	s.c.
8b	106	336	18	12
8d	146	440	38	5
8e	0	20	—	—
8f	0	618	—	—
8g	0	179	—	—
8h	0	0	—	—
10a	165	493	7	4
10k	229	676	19	12
11a	0	328	—	—
12b	70	238	47	17
12d	196	1300	24	7
12e	0	153	—	—
12i	100	256	52	37
14b	107	478	—	—
14d	132	384	20	3
14i	123	525	38	7
14j	123	548	12	3
15a	252	435	23	5
15b	382	523	22	7
17a	147	597	—	—
17b	522	946	12	1.5
17e	38	200	—	—
18k	0	174	—	—

[a] Non fasted, male, Charles Rivers CD1 mice were infected intraperitoneally with $2\sim9\times10^6$ cfu of *Staph. aureus* Smith contained in 0.5 ml of brain heart infusion broth. Compounds were administered as solutions or suspensions in 10% ethanol in hydroxypropylmethyl cellulose (p.o.) or pH 7.3 phosphate buffered saline (s.c.) at 1 and 5 hours post infection. The CD_{50} was calculated on the second day post infection as the total dose required to protect 50% of the mice from death.

acetylthiazole. The acetylthiazole (**17g**) was successfully prepared using triisopropylsilyl (TIPS) enol ether protection. After removal of the TMS protection, TES and TIPS groups were cleaved by treatment with tetrabutylammonium fluoride in the presence of an equivalent amount of acetic acid.

The acidic 2-proton of thiazole was protected as its TMS derivative[12], however, in our hands, after deprotonation at C-5, rapid silyl transfer occurred at -70°C. This was avoided by working at -90°C and using the aldehyde (**4b**) as electrophile.

We observed competitive deprotonation of 2-methylthiazole at the methyl group. Clean 5-anion could be obtained after bromination[13] at this position followed by bromine-lithium exchange and trapping with aldehyde (**4b**) at -90°C.

We found N-alkyl thiazolones were deprotonated in the 5-position with *n*-butyllithium and gave the required ketones (**18k** and **18l**) on reaction with **5b**. These anions appeared to have good stability and to be relatively unreactive, temperatures of -30 to 0°C being required for their reaction with the Weinreb reagent (**5b**).

Discussion

The present work was directed towards the identification of an agent which retains the oral absorption and potent antibacterial activity of mupirocin (**1a**) while lacking its metabolic instability. Lower human serum binding than that observed with mupirocin would also be seen as an advantage.

The *p*-methoxyphenyl ketone (**8b**) had appreciably better activity than the parent **6a**[6] while the *o*- and *m*-analogues were poorer. We therefore concentrated on *p*-substituted phenyl ketones. The *p*-hydroxyphenyl ketone (**8c**), a more polar analogue of **8b**, showed poorer antibacterial activity, especially against staphylococci. This is probably due to poor penetration into bacteria. The *o*-OH analogue (**6c**), while being much less polar than the *p*-analogue, had much poorer antibacterial activity, stressing the unfavourable nature of *ortho* substituents.

The antibacterial activities of several other substituted phenyl ketones were also better than that of the parent **6a**. We assessed pharmacokinetic behaviour in the mouse dosing p.o. and s.c. at 50 mg/kg. The two phenyl ketones with electron donating substituents **8b** and **8d** both gave moderate oral levels, but were highly serum bound. No oral levels were detected for the other examples. The trends in the s.c. levels were less clear, however, none of these aryl ketones appeared to be a potential systemic antibiotic. We therefore examined heterocyclic analogues.

The 3-furyl ketone (**10a**) had rather better antibacterial activity than the 2-isomer (**9a**)[6], had good murine pharmacokinetics and low human serum binding. Disappointingly, substitution with methoxy or acetyl groups gave compounds **10b** and **10g** with much poorer antibacterial activity. Perhaps this mirrors the situation with introduction of a *meta*-substituent in the phenyl ketones. Substitution with the smaller methyl group had a less deleterious effect on activity, but serum binding was dramatically increased. In general, we saw an approximate correlation between serum binding and polarity.

The unsubstituted pyridyl ketones (**11a**, **12a** and **13a**) also had low serum binding. The 3- and 4-isomers had better antibacterial activity than the previously reported[6] 2-pyridyl compound (**13a**), but were still too poorly active to be of interest. The 2-thienyl ketone (**15a**) was however rather more potent than the 3-isomer. An *electronegative* ring heteroatom adjacent to the point of attachment therefore appears to be detrimental to activity.

We chose to make analogues of the 3-pyridyl ketone (**12a**) into which introduction of a "*para*" substituent is possible. Electron donating lipophilic groups did give

improved activity although also raising serum binding. As in the phenyl ketone case an –SMe group gave poor pharmacokinetics, while the best overall levels were seen with the NMe_2 substituent.

Replacement of a second CH by N gave the pyrimidin-5-yl ketones (**14**). These were more polar, less serum bound compounds, of which **14d** and **14i** had interesting antibacterial activity and pharmacokinetic properties. The pyrrolidinyl analogue (**14j**) had a less attractive antibacterial spectrum, although significantly lower binding, than **14i**.

Comparison of the 2-thienyl ketones (**15a** and **15b**) with phenyl ketones (**6a** and **8b**) indicates that some improvement in antibacterial activity and pharmacokinetics may be achieved by replacement of a suitable CH=CH unit with sulphur. We therefore targeted the thiazolyl ketones (**17**) which are formally derived in this way from the pyridyl ketones (**12**).

The parent thiazolyl ketone (**17a**) had significantly better antibacterial activity than the pyridyl analogue (**12a**). In contrast to the furyl system, the serum binding of the parent thiazole (**17a**) and its methyl analogue (**17k**) were very similar. The antibacterial activity of **17k** was however marginally poorer than that of the parent. While the antibacterial activities of the nitrogen substituted thiazoles (**17d** and **17i**) were slightly disappointing, both the –SMe (**17e**) and –OMe (**17b**) analogues were highly active, with the methoxy compound having excellent murine pharmacokinetics. A further analogue (**17g**), having an electron withdrawing substituent had good antibacterial activity, although inferior to that of **17b**.

The thiazolonyl compound (**18k**), an isomer of **17b**, was the most polar example here described, but still had good antibacterial activity. Unfortunately it had poor murine pharmacokinetics. A less polar analogue (**18l**) had considerably poorer antibacterial activity, possibly due to the propyl group occupying the same space as a *meta* substituent on a phenyl ketone (**7**).

Compounds were selected on the basis of their antibacterial activities and mouse pharmacokinetic data for evaluation against an experimental mouse intraperitoneal sepsis caused by *Staphylococcus aureus* Smith. The results are shown in Table 2. The performance of these compounds in this infection model is reasonably consistent with their *in vitro* antibacterial activities, blood levels and serum binding. The two compounds (**10a** and **17b**) have the most potent curative effects. We note that the furan (**10a**) is distinguished by its low serum binding, while thiazole (**17b**) has especially good pharmacokinetics and *in vitro* potency against the infecting organism.

Conclusion

We have prepared a wide variety of aryl- and heteroaryl monic ketone derivatives, and found structural factors which influence *in vitro* antibacterial activity and murine pharmacokinetics. We have identified examples of monic ketones which show clear advantages over those previously revealed[6] in terms of antibacterial activity and human serum binding. Some of these agents gave murine infection model data which indicate that they may be useful systemic antibacterial agents for human use.

Experimental

^{1}H NMR data were recorded at 250 MHz on a Bruker AC-250F spectrometer using tetramethylsilane as standard. Infrared data were recorded on a Perkin-Elmer PE 983 machine, ultraviolet data on a Beckman DU 68 and mass spectra on a VG-ZAB spectrometer. The silica gel used for both normal phase thin layer (TLC) and column chromatography was Merck type 60. Tetrahydrofuran (THF) was distilled before use from sodium-benzophenone ketyl.

N-Methoxy-*N*-methyl-6,7,13-*O*-tris(trimethylsilyl)-monamide (**5b**)

N,*O*-Dimethyl hydroxylamine hydrochloride (17.5 g, 179 mmol) was dissolved in dichloromethane and aqueous sodium hydroxide (75 ml, 2.5 M). The aqueous layer was re-extracted with dichloromethane (3 × 50 ml) and the combined organic layers washed with saturated brine (25 ml). The organic layer was dried ($MgSO_4$) and added to monic acid isobutyl carbonic anhydride (87.2 mmol) and stirred at 20°C for 90 minutes.

The reaction mixture was cooled to 10°C and treated with triethylamine (75 ml, 538.1 mmol) and then chlorotrimethylsilane (68.3 ml, 538.1 mmol) dropwise over 15 minutes. After 10 minutes a catalytic amount of 4-*N*,*N*-dimethylaminopyridine was added, the mixture allowed to warm to room temperature and left stirring overnight.

The reaction was diluted with hexane, filtered, and the filtrate evaporated. The residue was taken up in hexane (500 ml), refiltered, and washed with saturated aqueous sodium bicarbonate, water and brine. After drying and evaporation the residue was taken up in hexane (120 ml) and allowed to crystallise at 0°C, to give the required product as a colourless crystalline solid (42.06 g, 80%) mp 78~79°C.

Anal Calcd for $C_{28}H_{57}NO_7Si_3$: C 55.7, H 9.5, N 2.3.
Found: C 56.0, H 9.7, N 2.3.

UV λ_{max} (EtOH) nm ε_m 222 (14,800). IR ν_{max} (KBr) cm^{-1} 1656, 1632. ^{1}H NMR (250 MHz, $CDCl_3$); δ 0.1 (s, 9H), 0.15 (s, 18H), 0.9 (d, J=7 Hz, 17-H_3), 1.2 (d, J=6.3 Hz, 14-H_3), 1.4, (1H, m, 12-H), 1.6 (1H, m, 8-H), 1.8 (1H, m, 9-H_2), 2.1 (1H, dd, J=11.6 and 14.6 Hz, 4-H), 1.15 (3H, s, 15-H_3), 2.55 (1H, d, J=14.6 Hz, 4-H), 2.7 (2H, m, 10- and 11-H), 3.2 (3H, s, NMe), 3.4 (1H, dd, J=2.3 and 8.8 Hz, 6-H), 3.5 (1H, d, J=11.3 Hz, 16-H), 3.7 (3H, s, OMe), 3.75~3.95 (4H, m, 5-, 7-, 13- and 16-H), 6.2 (1H, br s, 2-H). ^{13}C NMR (100 MHz, $CDCl_3$), δ 0.25, 0.5, 0.6 (SiMe), 12.5 (C-17), 19.0 (C-14), 20.9 (C-15), 32.2 (C-9), 32.5 (NMe), 42.1, 42.7 (C-8, 12), 43.2 (C-4), 55.3 (C-10), 59.4 (C-11), 61.4 (OMe), 65.5 (C-16), 70.5, 70.9, 73.3, 74.3 (C-5, 6, 7, 11), 115.7 (C-2), 153.5 (C-3),

168.1 (C-1).

The synthesis of ketone derivatives using Weinreb reagent (**5b**) is exemplified by that of (**10k**). Reactions using aldehyde (**4b**) were carried out using published procedures[4]. All other ketones and intermediates gave the expected ^{1}H and ^{13}C NMR, UV and IR spectra and were further characterised by high resolution EI-MS

{3-[5*S*-(2*S*,3*S*-Epoxy-5*S*-hydroxy-4*S*-methylhexyl)-3*R*,4*R*-dihydroxytetrahydropyran-2*S*-yl]-2-methylprop-1(*E*)-en-1-yl}2-methylfur-4-yl-ketone (**10k**)

To 5-tetrahydropyranyloxy pent-3-yn-2-one (**19**, 1.05 g, 5.8 mmol) in pentane (20 ml) at 0°C was added furan (4 ml) and 6 M hydrobromic acid (1.1 ml). The reaction was allowed to warm to room temperature and stirred for 2.5 hours. The organic layer was decanted off, the aqueous extracted with pentane (5 ml) and the combined organics dried ($MgSO_4$). The solution was distilled at atmospheric pressure through a Vigreux column to low volume, and pentane (2×6 ml) added and distilled to low volume. The residue was passed through a silica gel column, eluting with pentane. The product containing fractions were combined and distilled to low volume to give an oil (1.4 g). ^{1}H NMR indicates this to be a 6:4 mixture of pentane to 4-bromo-2-methylfuran by weight, 60% yield. NMR (250 MHz, $CDCl_3$) δ 7.25 (1H, s, 5-H), 6.0 (1H, s, 3-H), 2.3 (3H, s, Me).

The above furan was taken up in THF (10 ml), cooled to −70°C under argon and treated with ^{n}butyllithium in hexane (1.6 M, 2.0 ml). After 10 minutes at −70°C, the Weinreb reagent (**5b**) (1.208 g, 2 mmol) in THF (6 ml) was added dropwise.

After 30 minutes at −70°C acetic acid (0.24 g) in diethyl ether (50 ml), then water (30 ml), were added. The organic layer was dried ($MgSO_4$), evaporated, and purified by chromatography on silica gel eluting with 0~12% ethyl acetate in hexane. The product containing fractions were combined, evaporated at reduced pressure, and the residual oil in THF (25 ml) treated with 0.4 M HCl (6 ml) for 2 minutes. After quenching with sat. aq. $NaHCO_3$ (6 ml), the mixture was diluted with ethyl acetate (50 ml), and the aqueous layer extracted with ethyl acetate (50 ml). The combined organic layers were dried ($MgSO_4$), evaporated and the residue purified by chromatography eluting with 0~5% methanol in dichloromethane to yield the title compound (**10k**), (0.47 g, 58%) as a colourless foam. MS *m/z* 408 (M), 390 (M−H_2O), 121, 109 (ArCO); Found M^+, 408.2155. $C_{22}H_{32}O_7$ requires M 408.2148. UV λ_{max} (EtOH) nm ε_m 280 (7,000) sh, 255 (11,100), 217 (12,600). IR ν_{max} (KBr) cm^{-1} 3434, 2969, 2925, 1654, 1610, 1536. ^{1}H NMR (250 MHz, CD_3OD). δ 0.95 (3H, d, J=7 Hz, 17-H_3), 1.2 (3H, d, J=6.5 Hz, 14-H_3), 1.4 (1H, m, 12-H), 1.7 (2H, m, 9-H_2), 2.0 (1H, m, 8-H), 2.2, 2.3 (2×3H, 2×s, Furan-Me and 15-H_3), 2.2~2.35 (1H, m, 4-H), 2.7 (2H, m, 4- and 11-H), 2.8 (1H, dt, J=2.3, 5.8 Hz, 10-H), 3.4 (1H, dd, J=3.0, 9.0 Hz, 6-H), 3.6 (1H, d, J=11.5 Hz, 16-H), 3.7~3.95 (4H, m, 5-, 7-, 13- and 16-H), 6.35~6.6 (2×bs, 2-H and Furan-3-H), 8.1 (d, J=0.6 Hz, Furan-5-H). ^{13}C NMR (100 MHz, CD_3OD) δ 12.2, 13.3 (Furan Me and C-17), 20.2, 20.3 (C-14 and 15), 33.0 (C-9), 41.7, 43.7 (C-8 and 12), 44.2 (C-4), 56.9 (C-10), 61.3 (C-11), 66.4 (C-16), 70.0, 70.8, 71.6 (C-6, 7 and 13), 76.4 (C-5), 105.3 (Furan-C-3), 124.1 (C-2), 131.7 (Furan-C-4), 147.8 (Furan-C-5), 155.6, 158.6 (C-3 and Furan-C-2), 187.8 (C-1).

Acknowledgements

We would like to thank JOHN TURNER and GRAHAM WALKER for preliminary synthetic studies in this area.

References

1) FULLER, A. T.; G. MELLOWS, M. WOOLFORD, G. T. BANKS, K. D. BARROW & E. B. CHAIN: Pseudomonic acid: an antibiotic produced by *Pseudomonas fluorescens*. Nature 234: 416~417, 1971
2) MELLOWS, G.: Pseudomonic acid: its chemistry and metabolism. *In* Bactroban; Proceedings of an International Symposium. *Ed.*, R. L. DOBSON *et al.*, pp. 3~10, Excerpta Medica, Amsterdam, 1985
3) CLAYTON, J. P.; K. LUK & N. H. ROGERS: The Chemistry of pseudomonic acid. Part 2. The conversion of pseudomonic acid into monic acid A and its ethers. J. Chem. Soc. Perkin Trans. 1: 308~313, 1979
4) COULTON, S.; P. J. O'HANLON & N. H. ROGERS: The chemistry of pseudomonic acid. Part 4. $\alpha\beta$-Unsaturated ketones derived from monic acid A and its derivatives. J. Chem. Soc. Perkin. Trans 1: 729~734, 1982
5) FORREST, A. K.; P. J. O'HANLON & G. WALKER: The chemistry of pseudomonic acid. Part 12. Preparation of diazole and triazole derivatives. J. Chem. Soc. Perkin Trans. 1: 2657~2665, 1994
6) KLEIN, L. L.; C. M. YEUNG, P. KURATH, J. MAO, P. FERNANDES & P. LARLEY: Poster at 3rd Chemical Congress of North America, Toronto, June 1988
7) NAHME, S. & S. M. WEINREB: N-Methoxy-N-methylamides as effective acylating agents. Tetrahedron Lett. 22: 3815~3818, 1981
8) ZHENG, J. & K. UNDHEIM: Organocerium (III) reagents from pyridine in carbon bond forming reactions. Acta Chem. Scand. 43: 816~818, 1989
9) GSCHWEND, H. W. & H. R. RODRIGUEZ: Heteroatom-facilitated lithiations. Organic Reactions 26: 1~360, 1979
10) EMDE, H. *et al.*: Trialkylsilyl perfluoroalkanesulfonates: highly reactive silylating agents and Lewis acids in organic synthesis. Synthesis: 1~26, 1982
11) OBRECHT, D.: Acid catalysed reactions of substituted acetylenic ketones: a new approach for the synthesis of 3-halofurans, flavones and styrylchromens. Helv. Chim. Acta 72: 447~456, 1989
12) DONDONI, A.: Synthetic aspects of the chemistry of silylthiazoles and silyloxazoles. Lect. Heterocycl. Chem. 8: 13~20
13) GAWAPATHI, K. & D. K. KULKARNI: Chemistry of the thiazoles IV. Bromination and nitration of some monosubstituted thiazoles. Proc. Ind. Acad. Sci. 37A: 758~764, 1953