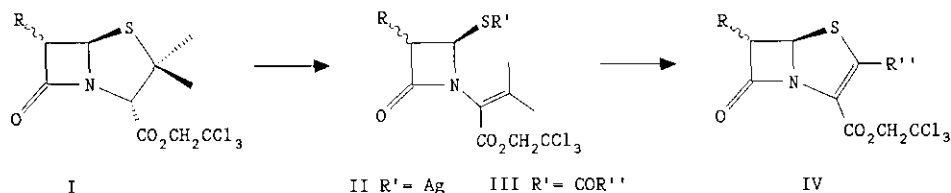


REACTIVITY PARAMETERS OF THE METAL ASSISTED 1,2-CLEAVAGE OF PENICILLINS

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Abstract - A straightforward and smooth conversion of penicillins into 1,2-secopenicillanates is described. The thiazolidine ring opening is brought about by the co-operative effect of strong non-nucleophilic bases and thiophilic heavy metal salts. The nature of the latter and the polarity of the solvent profoundly affect the reaction rate. Best general conditions can be drawn for the conversion of numerous 6-substituted penicillanates with various protecting groups on the carboxy function.

Recently we¹ reported the shortest synthesis of penems from a natural substrate. The route exploited an innovative 1,2-cleavage of penicillins I to secopenicillanates II, which were *in situ* acylated to azetidinones III. Ozonolysis of the latter and C=O/C=O reductive coupling afforded penems IV.²



The key step, *i.e.* the transformation of I into secopenicillanates III, was realized in a short, practical and efficient way in comparison with previous methods.^{3a-n} Being a formal β elimination, the thiazolidine ring opening smoothly occurred in the presence of a strong non-nucleophilic base (DBN) and thiophilic heavy metal salt (AgNO_3).

The apparent major drawback was the poor reactivity of many penam substrates. To overcome this limitation we started a deeper investigation on the reactivity

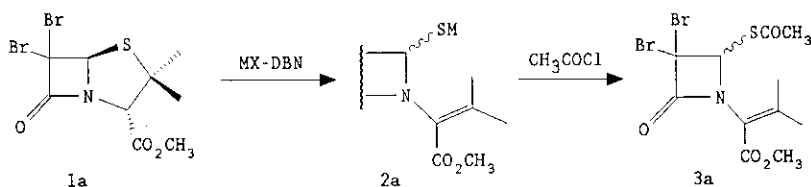
parameters. The whole matter was tackled by examining one variable at a time. Hereafter influences exerted by the heavy metal salt, solvent, base, penicillin carboxy protecting group and C-6 substituent are detailed.

Methyl 6,6-dibromopenicillanate⁴ **1a**, was chosen as a model substrate, because of its easy availability and the challenging poor reactivity under the conditions of the previous work (AgNO_3 -DBN, CH_3CN). In order to assess how the reaction rate of **1a** would be affected by the kind of the heavy metal reagent and reaction solvent, experiments were carried out monitoring the starting material depletion, while the preparative value of the reaction was appreciated by the isolated yields of thioester **3a**⁵ obtained after in situ acetylation of the thiolate **2a** (Table 1). This methodology avoided the bias caused by the isolation of different metal 1,2-secopenicillanates; e.g. mercury derivatives (**2a**, $\text{M}=\text{Hg}$ or HgPh) can be easily purified by SiO_2 chromatography, while losses are associated with the isolation of the more polar silver thiolate (**2a**, $\text{M}=\text{Ag}$) either by chromatographic methods or solvent extraction ($\text{C}_2\text{H}_5\text{OAc}$ /water).

A dramatic influence of the heavy metal salt (CH_3CN as solvent) and of the reaction solvent ($\text{MX}=\text{AgOAc}$) on the reaction rate is evident from Table I, where results are ranked in order of decreasing reactivity. As far as the heavy metal thiophile is concerned, the performance of the first entries when compared to the previously used¹ silver nitrate is noteworthy, with obvious implications from a preparative point of view. Silver salts were studied in detail compared with Hg(I) or Hg(II) counterparts owing to the minor environmental problems connected, in prospect, to large scale applications. The apparent drawback of their cost is minimized by the almost quantitative recovery of the precious metal after work-up. In particular, silver chloride is quite remarkable, since it acts overall as a catalyst, being recovered unchanged (and successfully recycled, if desired)⁶ after acylation.

Cu(I) and Pb(II) salts, that were scrutinized as alternative thiophilic reagents, resulted in poor reactivity and overwhelming side-reactions. Although the better ability of silver and mercury to coordinate thioethers⁷ can be invoked to explain the effects observed on varying the metal, any attempt to rationalize the metal counterion effect has been fruitless so far.

A survey of Table 1 also reveals the important role played by the solvent on the reaction rate. Extremely fast reactions were generally observed when polar aprotic solvents were used, nevertheless no linear relationship could be drawn

Table 1 - Influence¹ of the heavy metal salt and solvent on the rate of formation of 2a

 Heavy Metal Salt Effect
(Solvent = CH₃CN)

 Solvent Effect
(Heavy metal salt = AgOAc)

Heavy Metal Salt Effect (Solvent = CH ₃ CN)				Solvent Effect (Heavy metal salt = AgOAc)			
MX	Time ²	Yield (%)		Solvent	Time ²	Yield (%)	
Ag ₂ O	2 min	72		Pyridine	2 min	86	
Ag ₂ CO ₃	4 min	61		DMSO	6 min	-	
AgCl	8 min	78		DMA	8 min	85	
PhHgCl	12 min	85		HMPA	8 min	82	
AgSCN	20 min	78		DMF	10 min	61	
HgO	40 min	21		Acetone	45 min	55	
AgF	50 min	81		CH ₃ CN	2 h	77	
Hg ₂ Cl ₂	1.8 h	94		EtOAc	4 h	18	
AgOAc	2 h	77		Dioxane	6.5 h	47	
Ag hexanoate	2 h	73		Benzene	8 h	70	
Ag salicylate	24 h	55		CH ₂ Cl ₂	24 h	88	
AgNO ₃	40 h	83		Ethyl formate	30 h	59	
AgClO ₄	>2 days	45		ClCH ₂ CH ₂ Cl	48 h	66	

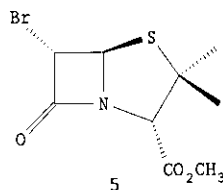
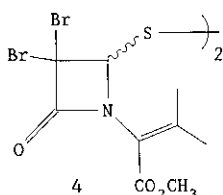
1) Experiments were performed as follows:

A mixture of the selected heavy metal salt (1.3 mmol) and 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) (1.2 mmol) in the organic solvent (sieve-dried, 5 ml) was stirred 2 min under nitrogen before addition of methyl 6,6-dibromopenicillanate 1a (1.0 mmol). Stirring was continued at room temperature until depletion ($\geq 95\%$) of penicillanate. Acetyl chloride (2 mmol) was then injected, while keeping the temperature at 15-20°C. After 15 sec. the reaction mixture was filtered and poured into ethyl ether-H₂O. The organic layer was dried over Na₂SO₄ and evaporated to afford the crude thioester 3a which was purified by flash chromatography on silica gel (cyclohexane - ethyl acetate mixtures as eluants).

 2) Time corresponding to $\geq 95\%$ depletion of 1a

between reactivity and polarity descriptors.

In many cases, even for very fast reactions, clean production of the intermediate silver thiolate **2a** (M=Ag) was assessed by the isolation of thioester **3a** in good to excellent yield. Prevalent formation of tars occurred when operating with ethyl acetate as well as with ethyl ether, carbon tetrachloride and xylene. Performing the reaction in DMSO apparently (tlc) gave the expected intermediate salt **2a** (M=Ag), but after quenching with CH_3COCl , the symmetrical disulphide **4**^a was isolated in 75% yield.



Use of AgOAc/DBN in nitromethane caused predominant monobromination of **1a**, methyl 6- α -bromopenicillanate **5**^a being produced in more than 50% yield after 3 h at room temperature. Organic bases alternative to DBN have been screened on substrate **1a** with silver acetate as thiophile and acetonitrile as solvent. Practically no reaction occurred with triethylamine, pyridine and dimethylaminopyridine (DMAP) after 8 h at room temperature, thus suggesting the inefficiency or the limited value of tertiary aliphatic and aromatic amines. On the contrary 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and 1,1,3,3-tetramethylguanidine^a approximately doubled the reaction rate relative to DBN; in addition, by-products were minimized and thioester **3a** could be isolated in somewhat higher yield. These findings corroborate our original hypothesis¹ that strong non-nucleophilic bases, as ad hoc substituted amidines and guanidines, are needed to accomplish the β elimination step.

At this point, backed by the knowledge of the main reactivity parameters, we were eased to face problems connected with structural variation of the substrate, namely ester typology and C-6 substitution.

Starting from 6,6-dibromopenicillanic acid¹⁰ the most common carboxy protecting groups in β -lactam chemistry were introduced on the carboxy function uneventfully affording penicillanic esters **1b-i**.^a These were subjected to the action of AgOAc/DBN complex (or, for less reactive esters, to PhHgCl/DBN) in CH_3CN and, following quenching with CH_3COCl , thioesters **3b-i** were isolated in good to excellent yields (75-95%) (Table 2).

Table 2 - Influence^{1,3} of the ester moiety on the 1,2-cleavage of penicillanates

1a-i

$\xrightarrow[2) \text{CH}_3\text{COCl}]{1) \text{MX/DBN}}$

3a-i

1b R=CH₂CCl₃

1c R=CH₂OCOCH₃

1d R=CH₂CH=CH₂

1e R=CH₂

1f R=CH₂

1g R=CH₂CH₂Si(CH₃)₃

1h R=CH()₂

1i R=C(CH₃)₃

Substrate	MX	Time ²	Substrate	MX	Time
1b	AgOAc	1 min	1g	AgOAc	3.5 h
1c	"	15 min	1h	PhHgCl	3 h
1d	"	45 min	1i	"	6.5 h
1e	"	1 h	1a	AgOAc	2 h
1f	"	2.3 h	"	PhHgCl	12 min

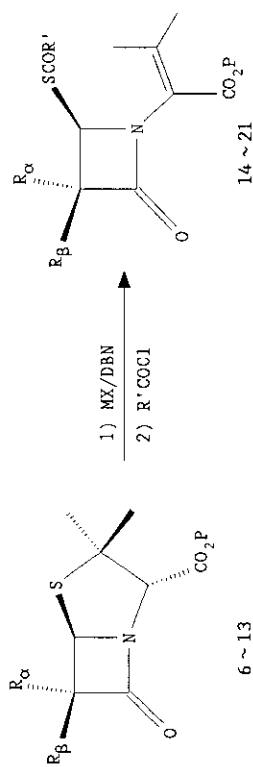
1) See Footnote 1, Table 1 for general reaction conditions.

2) Time required for ≥95% depletion of starting 1a-i

3) For all substrates isolated yields of thioester 3 were in excess of 75%.

As expected, electron withdrawing carboxylates induced faster ring-opening reactions, the observed reactivity order on varying R being CH₂CCl₃ > CH₂OCOCH₃ > CH₂CH=CH₂ ≥ CH₂ > CH₂ > CH₂CH₂Si(CH₃)₃ > CH()₂ > C(CH₃)₃, but all of the esters, independently of the reactivity evidenced, smoothly underwent the thiazolidine ring cleavage with high material balance.

Having refined the experimental conditions of the cleavage reaction by operating on 6,6-dibromopenicillanates we turned our attention to the influence of the C₆ sidechain. The range of substituents examined in our preliminary work has been broadly extended, as it can be appreciated by a survey of Table 3. Reported yields refer to unoptimized experimental conditions, which should be tailored for each individual substrate; nevertheless the potentiality and broadness in scope of the method is testified by its successful application to 6,6-disubstituted and 6α- or 6β-alkyl, 6α-halo-, 6α-alkoxy-, 6α-acyloxy-, 6β-alkylamino- and 6β-acylamino-substituted penam derivatives.¹¹ The opening reaction is favoured by electron withdrawing substituents; free -OH or >NH functions do

Table 3 - Influence of the C₆-sidechain on the 1,2-cleavage/acylation of penicillanates

Penam Substrate			Ring-Opening/Acylation Conditions			4-Azetidinonyl-Thioester Product					
#	R ¹ _α	R ¹ _β	P ¹	MX	Time ^{2,3} (h)	R ¹	#	yield (%)	Selected Spectroscopic Data		
									ir (CHCl ₃) ν _{max} (cm ⁻¹)	¹ H nmr (CDCl ₃) δ(J, Hz)	
									H-3	H-4	
6a	Et	(R)-CH(CH ₃)OTBMS	TCE	AgNO ₃	2.5	CH ₃ OTBMS	14a	79	1780, 1725, 1700	-	6.10 (s)
6b	"	(R)-CH(CH ₃)OCO ₂ TCE	"	"	4	"	14b	80	1790-1760, 1735, 1710	-	6.23 (s)
6c	"	(R)-CH(CH ₃)OTBMS	AcOH	AgCl	0.5 (-25°C)	CH ₃	14c	82	1780-1750, 1700	-	6.03 (s)
6d	"	(R)-CH(CH ₃)OH	"	"	"	"	14d	81		-	6.02 (s)
7	H	(R)-CH(CH ₃)OTBMS	TCE	PhHgCl	2	"	15	96	1765, 1740, 1695	3.60 (dd, J=3.5, 5.5)	5.97 (d, J=5.5)
8a	(S)-CH(CH ₃)OTBMS	Br	AcOH	AgNO ₃	12	"	16a	74	1780-1750, 1700	-	5.88 (s) (CCl ₄)
8b	"	"	BZH	"	72	"	16b	71	1778, 1722, 1705	-	5.83 (s)
9a	(R)-CH(CH ₃)OTBMS	H	"	AgNO ₃	60 (0°C)	"	17a	60	1760, 1735, 1692	3.22 (dd, J=2.3, 6.3)	5.73 (d, J=2.3)
"	"	"	"	PhHgCl	2	"	"	80	"	"	"
9b	"	"	Me	AgCl	4 (DMA)	"	17b	55	1755, 1725, 1700	3.18 (dd, J=2.6, 6)	5.70 (d, J=2.6)
"	"	"	"	Ag ₂ O	5	"	"	49	"	"	"
9c	"	"	PMB	AgCl	4 (DMA)	CH ₃ OCOCH ₂ CH ₂ CH ₃	17c	51	1755, 1710	3.20 (dd, J=2.5, 5.5)	5.22 (d, J=2)
9d	(R)-CH(CH ₃)OTBMS	"	AcOH	"	0.2	"	17d	60	1750(vs), 1700	3.22 (dd, J=2.5, 5.5)	5.69 (d, J=2.5)
9e	(R)-CH(CH ₃)OH	"	"	"	0.5 (0°C)	"	17e	62	1750(vs), 1695	3.23 (dd, J=2.5, 6)	5.65 (d, J=2.5)
10a	CH ₃ CH ₂ CH ₃	"	PMB	"	6	CH ₃ COCH ₃	18a	33	1755, 1705	3.19 (m)	5.36 (d, J=2)
10b	CH ₃ CH ₂ OCOCH ₃	"	PMB	"	1	"	18b	72	1755, 1725, 1700 (sh)	3.27 (m)	5.41 (d, J=2.1)
10c	CH ₃ CH ₂ OCO ₂ PMB	"	"	"	0.5	"	18c	66	1760, 1725(sh), 1700(sh)	3.33 (m)	5.40 (d, J=2.2)

Table 3 - continued

Penam Substrate			Ring-Opening/Acylation Conditions			4-Azetidinonyl-Thioester Product			
#	R _G ¹	R _β ¹	P ¹	MX	Time ^{2,3} (h)	R ¹	#	Yield (%)	Selected Spectroscopic Data ir(CHCl ₃) ν _{max} (cm ⁻¹) ¹ H nmr (CDCl ₃) δ(J, Hz) H-3 H-4
10d	CH ₃ CH ₂ OTBDPS	H	PMB	AgCl	2	CH ₃ OCH ₃	18d	74	1755, 1720, 1695(sh) 3.43(m) 5.45 (d, J=2)
11a	H	"	TCE	AgNO ₃	60(0°C)	"	19a	52	α:3.53(dd, J=5, 15) 5.78 (m) β:2.95(dd, J=2, 5, 15)
11b	"	"	BN	AgCl	2	CH ₃ Ph	19b	52	α:3.46(dd, J=5, 1, 15, 6) 5.65 (dd, J=2, 7, 5, 1) β:2.93(dd, J=2, 7, 15, 6)
11c	F	"	TCE	"	4	CH ₃ OCH ₃	19c	40	1777, 1734, 1710 5.53(dd, J=2, 54) 5.89(dd, J=2, 11)
11d	Cl	"	PMB	AgCl	0.2	"	19d	28	1785, 1725, 1680(sh) 4.78 (d, J=2, 1) 5.60 (d, J=2, 1)
11e	Br	"	TCE	AgNO ₃	60(0°C)	"	19e	86	1785, 1735, 1710 4.85 (d, J=2) 5.85 (d, J=2)
11f	OTBDPS	"	PMB	PhHgCl	1	CH ₃ OPh	19f	76	1770, 1715, 1695 4.81 (d, J=2) 5.45 (d, J=2)
11g	OCO ₂ TCE	"	TCE	"	0.2	CH ₃	19g	41	1786, 1732, 1705 5.82 (d, J=2) 5.68 (d, J=2, 8) ^a
11h	OCOCH ₃	"	PMB	"	0.5	CH ₃ OPh	19h	75	1784, 1758, 1725-1695 5.62 (2H, s)
11i	OCOCH ₃ OPh	"	"	AgOAc	0.2	"	19i	39	1780, 1720, 1700(sh) 5.77 (d, J=2) 5.68 (d, J=2) ^a
11j	"	"	ACM	AgCl	0.04	"	19j	63	1775, 1740(sh), 1695 5.80 (d, J=2) 5.72 (d, J=2) ^a
11k		"	PMB	"	0.2	CH ₃ OCH ₃	19k	51	1765, 1740-1690(sh) 5.24 (d, J=2) 5.69 (d, J=2) ^a
12a	H	HCOCH ₃ OPh	TCE	PhHgCl	0.5	CH ₃	20a	60	1775, 1732, 1698 5.32(dd, J=5, 8) 6.11 (d, J=5)
12b	"	"	PMB	AgOAc	6	"	20b	78	1775, 1730, 1695 4.66(dd, J=4, 5, 8) 5.44 (d, J=4, 5)
12c	"	MHCPH ₃	"	AgCl	3.5	"	20c	63	1760, 1708 6.32(d, J=5, 5) 5.82 (d, J=5, 5)
13	"	Phth	TCE	PhHgCl	4	"	21 ^b	18	1775, 1725, 1700(sh)

1) Abbreviations are as follows: TBDPS = tert-butyldimethylsilyl; TBDPS = tert-butyldiphenylsilyl; TMS = trimethylsilyl; TCE = trichloroethyl; ACM = acetoxymethyl; PMB = p-methoxybenzyl; PMB = p-methoxybenzyl; BN = benzyl; BZn = benzhydryl; Me = methyl; Phth = phthalimido.

2) Reaction time before quenching with R¹OC(=O)Cl

3) General reaction conditions are as detailed in Footnote 1, Table 1, (CH₃CN as solvent) unless otherwise stated.

4) Attribution of the ¹H nmr signals due to H-3 and H-4 of the β-lactam ring could be reversed.

5) In addition 68% of C-3 epimer was formed (see Text).

not interfere. Performing the reaction in DMA, as predictable from the study on the solvent influence, accelerates the reaction rate. Operating at lower temperature, though it requires longer reaction time, often had a beneficial effect on the final yield.

A final mention should be made of the stereoselectivity of the ring opening process. No epimerization at C₃ or C₄ (azetidinone numbering) was ever observed, apart from the case of 6,6-dibromo (1a-i) and 6β-phthalimido (13) substrates. The latter, under the conditions stated in Table 3, afforded a 1:4 mixture of "cis" (3R) thioester 21 and its C₃ epimer (3S). The increased acidity of the proton adjacent to the phthalimido group (and α to the β-lactam carbonyl) facilitates its removal by DBN and thus accounts for the preferential formation of the less sterically congested trans arrangement on the β-lactam ring. Substituting an acylamino or, even better, a tritylamino for the phthalimido group, avoided the C₃ epimerization to take place (Table 3; entries 12a-c). Various degrees of epimerization at C₄ [leading in some cases to completely racemic thioester products] were uncovered^{1,2} in the ring-opening reaction of 6,6-dibromopenicillanates (1a-1) by using (R)- and (S)-Mosher's acid chlorides^{1,3} as the acylating agents. This fact was undetected at the time of our preliminary communication¹ and spurred a series of experiments aimed at elucidating the reaction mechanism and by-products which will be reported in due time. Further work confirmed the C₄-epimerization to be restricted to the dibromo substrate and the enantiomeric purity of the products reported in Table 3 was confirmed.

In conclusion, the reactivity parameters of the heavy metal assisted 1,2-cleavage of penicillins were explored, and the best general conditions for their conversion into synthetically useful 1,2-secopenicillanates were found. This reaction favourably compares with any other ring-opening reaction leading to azetidinonyl thioesters^{3a-n} for scope, stereoselectivity, yields and straightforwardness.

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4. Compounds **1a-i** (crystals, unless otherwise stated) were prepared by the following methods : **1a** : See R. G. Micetich, S. N. Maiti, M. Tanaka, T. Yamazaki, and K. Ogawa, J. Org. Chem., 1986, **51**, 853. **1b** : From 6,6-dibromopenicillanic acid¹⁰ (DBPA) with pyridine (2.5 eq.) and ClCOOCH₂CCl₃ (2.0 eq.) in EtOAc (2 h, -10°C to room temperature, 93% yield), mp 86-88°C; ir (nujol) $\nu_{\max}$ 1800, 1760 cm⁻¹; ¹H nmr (CDCl₃) δ 1.56(3H,s), 1.67(3H,s), 4.68(1H,s), 4.80(2H,s), 5.83(1H,s). Anal. Calcd for C₁₀H₁₀Br₂Cl₃NO₃S : C, 24.49; H, 2.06; N, 2.86; S, 6.54. Found: C, 24.78; H, 2.23; N, 2.95; S, 6.48. **1c** : From DBPA with NaHCO₃ and BrCH₂OCOCH₃ (2 eq. each) in DMF (5°C, 30 min, thence 20 h at room temperature, 86%), mp 83-84°C; ir (nujol) $\nu_{\max}$ 1780, 1750, 1740 cm⁻¹; ¹H nmr (CDCl₃) δ 1.47(3H,s), 1.61(3H,s), 2.09(3H,s), 4.54(1H,s), 5.78(1H,s), 5.80(2H,s). Anal. Calcd for C₁₁H₁₃Br₂NO₃S : C, 30.65; H, 3.04; N, 3.25; S, 7.44. Found: C, 30.59; H, 3.05; N, 3.31; S, 7.51. **1d** : From DBPA with NEt₃ and allyl bromide (1.5 eq. each) (0°C, overnight, 83%), oil; [α]_D + 186° (c 2.0, CHCl₃); ir (CHCl₃) 1790, 1735 cm⁻¹; ¹H nmr (CDCl₃) δ 1.27(3H,s), 1.62(3H,s), 4.53(1H,s), 4.63(2H,m), 5.2-5.5(2H,m), 5.79(1H,s), 5.90(1H,m); fdms (EHC= 0 mA), m/z 397, 399, 401 (51, 100, 44, M⁺). **1e** : See I. Ganboa and C. Palomo, Synthesis, 1986, 52. **1f** : From DBPA, with NEt₃ and p-methoxybenzyl chloride (1.5 eq. each) in DMF (overnight,

75%), mp 90-91°C; ir (KBr) $\sqrt{\text{max}}$ 1795, 1745 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.53(3H,s), 1.60(3H,s), 3.80(3H,s), 4.51(1H,s), 5.13(2H,s), 5.77(1H,s), 6.86(2H,d,J=8.5 Hz), 7.32(2H,d,J=8.5 Hz). Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{Br}_2\text{NO}_4\text{S}$: C, 40.10; H, 3.58; N, 2.92; S, 6.69. Found: C, 39.98; H, 3.70; N, 2.97; S, 6.62. **1g**: From DBPA with pyridine (2 eq.), phenyl dichlorophosphate (1.5 eq.) and trimethylsilylethanol (1 eq.) in dioxane (5 h, 10°C to room temperature, 87%), mp 94-95°C; ir (KBr) $\sqrt{\text{max}}$ 1800, 1730 cm^{-1} ; ^1H nmr (CDCl_3) δ 0.08(9H,s), 0.9-1.1(2H,m), 1.47(3H,s), 1.61(3H,s), 4.2-4.4(2H,m), 4.48(1H,s), 5.80(1H,s); $[\alpha]_D + 168^\circ$ (c 1.5, CHCl_3). Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{Br}_2\text{NO}_3\text{SSi}$: C, 34.00; H, 4.61; N, 3.05; S, 6.98. Found: C, 34.10; H, 4.67; N, 3.08; S, 7.14. **1h**: See G. Sacripante and G. Just, *J. Org. Chem.*, 1987, 52, 3659. **1i**: By treating the crude solution of 6,6-dibromopenicillanyl chloride (from DBPA, NEt_3 , PCl_5 , 1 eq. each, CH_2Cl_2 1 h at 0°C) with excess t-butyl alcohol and CaCO_3 (2 h, 55%), mp 133-134°C; ir (film) $\sqrt{\text{max}}$, 1798, 1735 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.48(12H,s), 1.57(3H,s), 4.38(1H,s), 5.71(1H,s). Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{Br}_2\text{NO}_3\text{S}$: C, 34.72; H, 4.13; N, 3.37; S, 7.72. Found: C, 34.89; H, 4.27; N, 3.52; S, 7.75.

5. Selected physical data for secopenicillanates **3a-i**, **4** (isolated as white powders, unless otherwise stated) are as follows: **3a**: Ir (CHCl_3) $\sqrt{\text{max}}$ 1792, 1720 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.97(3H,s), 2.30(3H,s), 2.44(3H,s), 3.81(3H,s), 6.23(1H,s); oil. Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{Br}_2\text{NO}_4\text{S}$: C, 31.83; H, 3.16; N, 3.37; S, 7.72. Found: C, 32.21; H, 3.11; N, 3.46; S, 7.61. **3b**: Ir (CHCl_3) $\sqrt{\text{max}}$ 1797, 1745, 1720 cm^{-1} ; ^1H nmr (CDCl_3) δ 2.07(3H,s), 2.36(3H,s), 2.45(3H,s), 4.87(2H,s), 6.33(1H,s); mp 90-94°C. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{Br}_2\text{Cl}_3\text{NO}_4\text{S}$: C, 27.07; H, 2.27; N, 2.63; S, 6.02. Found: C, 27.15; H, 2.28; N, 2.62; S, 6.11. **3c**: Ir (CHCl_3) $\sqrt{\text{max}}$ 1780-1750, 1735-1700 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.91(3H,s), 2.07(3H,s), 2.23 (3H,s), 2.33(3H,s), 5.78(2H,ABq,J= 6Hz), 6.13(1H,s); mp 96-99°C; fdms (EHC= 0 mA), m/z 471, 473, 475 (44, 100, 50, M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{Br}_2\text{NO}_6\text{S}$: C, 33.00; H, 3.20; N, 2.96; S, 6.78. Found: C, 33.05; H, 3.31; N, 2.88; S, 6.74. **3d**: Ir (CHCl_3) $\sqrt{\text{max}}$ 1778, 1705 cm^{-1} ; ^1H nmr (CDCl_3) δ 1.95(3H,s), 2.30(3H,s), 2.43(3H,s), 4.72(2H,m), 5.2-5.6 (2H,m), 5.8-6.2(1H,m), 6.28(1H,s); mp 69-71°C; fdms (EHC= 0 mA), m/z 439, 441, 443 (59, 100, 59, M^+). Anal. Calcd. for $\text{C}_{13}\text{H}_{15}\text{Br}_2\text{NO}_4\text{S}$: C, 35.40; H, 3.43; N, 3.18; S, 7.27. Found: C, 35.61; H, 3.49; N, 3.20; S, 7.22. **3e**: Ir (CHCl_3) $\sqrt{\text{max}}$ 1790, 1720, 1708 cm^{-1} ; ^1H nmr (CDCl_3) δ 2.01(3H,s), 2.33(3H,s), 2.43(3H,s), 5.31(2H,s), 6.15(1H,s), 7.55(2H,d,J= 8.5Hz), 8.25(2H,d,J= 8.5Hz); mp 83-86°C; fdms (EHC= 0 mA), m/z

- 534, 536, 538 (55, 100, 52, M⁺). Anal. Calcd for C₁₇H₁₆Br₂N₂O₆S : C, 30.08; H, 3.01; N, 5.22; S, 5.98. Found : C, 29.98; H, 3.03; N, 5.22; S, 5.89. **3f** : Ir (CHCl₃) $\sqrt{\text{max}}$ 1778, 1700 cm⁻¹; ¹H nmr (CDCl₃) δ 1.90(3H,s), 2.24(3H,s), 2.34(3H,s), 3.74(3H,s), 5.13(2H,s), 6.13(1H,s), 6.38(2H,d,J= 8.6Hz), 7.33(2H,d,J= 8.6Hz); oil; fdms (EHC= 0 mA), m/z 519, 521, 523 (47, 100, 49, M⁺). **3g** : Ir (CHCl₃) $\sqrt{\text{max}}$ 1770, 1700 cm⁻¹; ¹H nmr (CDCl₃) δ 0.04(9H,s), 0.8-1.3 (2H,m), 1.91(3H,s), 2.19(3H,s), 2.37(3H,s), 3.9-4.4(2H,m), 6.23(1H,s); oil; fdms (EHC= 0 mA), m/z 499, 501, 503 (56, 100, 66, M⁺). **3h** : Ir (CHCl₃) $\sqrt{\text{max}}$ 1790, 1717 cm⁻¹; ¹H nmr (CDCl₃) δ 1.97(3H,s), 2.27(3H,s), 2.35(3H,s), 6.10(1H,s), 6.88(1H,s), 7.33(10H,s); oil; fdms (EHC= 0 mA), m/z 455, 457, 459 (48, 100, 51, M⁺). **3i** : Ir (KBr) $\sqrt{\text{max}}$ 1792, 1780, 1710, 1660 cm⁻¹; ¹H nmr (CDCl₃) δ 1.60(9H,s), 1.92(3H,s), 2.27 (3H,s), 2.45(3H,s), 6.25(1H,s); mp 105-108°C. Anal. Calcd for C₁₄H₁₉Br₂NO₄S : C, 36.78; H, 4.19; N, 3.06; S, 7.01. Found: C, 37.12; H, 4.28; N, 2.97; S, 6.88. **4** : Ir (CHCl₃) $\sqrt{\text{max}}$ 1780, 1730 cm⁻¹; ¹H nmr(CDCl₃) δ 2.01(3H,s), 2.33(3H,s), 3.80(3H,s), 5.63(1H,s); foam. Anal. Calcd for C₁₈H₂₀Br₄N₂O₆S₂ : C, 29.05; H, 2.71; N, 3.76; S, 8.62. Found: C, 29.36; H, 2.83; N, 3.93; S, 8.40.
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