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

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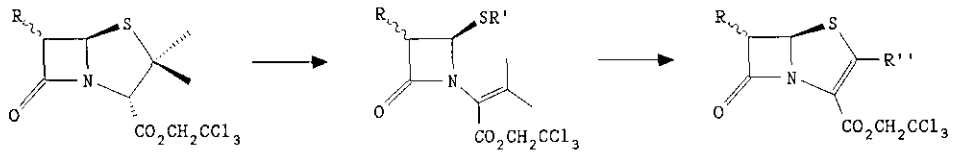
Abstract - A straightforward and smooth conversion of penicillins into 1,2-secopenicillanates is described. The thiazolidine ring opening is brought about by the co-operative effect of strong non-nucleophilic bases and thiophilic heavy metal salts. The nature of the latter and the polarity of the solvent 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 we[1] 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]



I II R'= Ag III R'= COR'' IV

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-h] Being a formal ß 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.

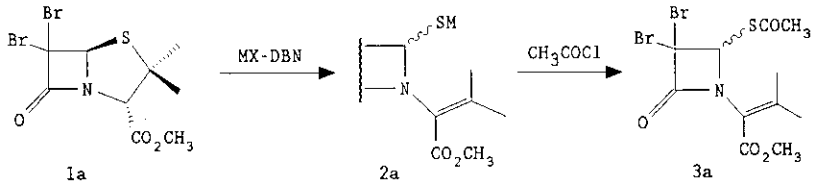
Methyl 6,6-dibromopenicillanate[4] **1a**, was chosen as a model substrate, because of its easy availability and the challenging poor reactivity under the conditions of the previous work ($AgNO_3$-DBN, CH_3CN). In order to assess how the reaction rate of **1a** would be affected by the kind of the heavy 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**, M=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**, M=Ag) either by chromatographic methods or solvent extraction (C_2H_5OAc/water).

A dramatic influence of the heavy metal salt (CH_3CN as solvent) and of the reaction solvent (MX=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 used[1] 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 succesfully 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 thioethers[7] 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 - Influence[1] of the heavy metal salt and solvent on the rate of formation of **2a**



1a 2a 3a

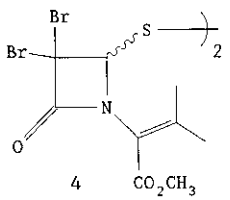
Heavy Metal Salt Effect (Solvent = CH_3CN)				Solvent Effect (Heavy metal salt = AgOAc)			
MX	Time[2]		Yield (%)	Solvent	Time[2]		Yield (%)
Ag_2O	2	min	72	Pyridine	2	min	86
Ag_2CO_3	4	min	61	DMSO	6	min	-
AgCl	8	min	78	DMA	8	min	85
PhHgCl	12	min	85	HMPA	8	min	82
AgSCN	20	min	78	DMF	10	min	61
HgO	40	min	21	Acetone	45	min	55
AgF	50	min	81	CH_3CN	2	h	77
Hg_2Cl_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_2Cl_2	24	h	88
$AgNO_3$	40	h	83	Ethyl formate	30	h	59
$AgClO_4$	>2	days	45	$ClCH_2CH_2Cl$	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 (≥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-H_2O. The organic layer was dried over Na_2SO_4 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 ≥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**[5] was isolated in 75% yield.



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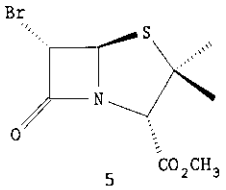

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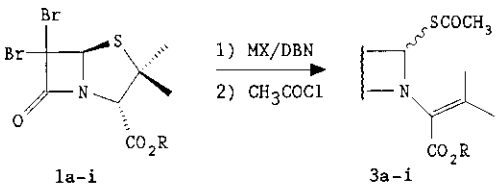
Use of AgOAc/DBN in nitromethane caused predominant monodebromination of **1a**, methyl 6-α-bromopenicillanate **5**[6] being produced in more than 50% yield after 3 h at room temperature. Organic bases alternative to DBN have been screened on substrate **1a** with silver acetate as thiophile and acetonitrile as solvent. Practically no reaction occurred with triethylamine, pyridine and dimethylamino-pyridine (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[9] 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 hypothesis[1] that strong non-nucleophilic bases, as ad hoc substituted amidines and guanidines, are needed to accomplish the ß 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 acid[10] the most common carboxy protecting groups in ß-lactam chemistry were introduced on the carboxy function uneventfully affording penicillanic esters **1b-i**.[4] 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 3a-i

1b R=CH_2CCl_3 1c R=CH_2OCOCH_3 1d R=$CH_2CH=CH_2$ 1e R=CH_2-C6H4-NO_2

1f R=CH_2-C6H4-OCH_3 1g R=$CH_2CH_2Si(CH_3)_3$ 1h R=$CH(C_6H_5)_2$ 1i R=$C(CH_3)_3$

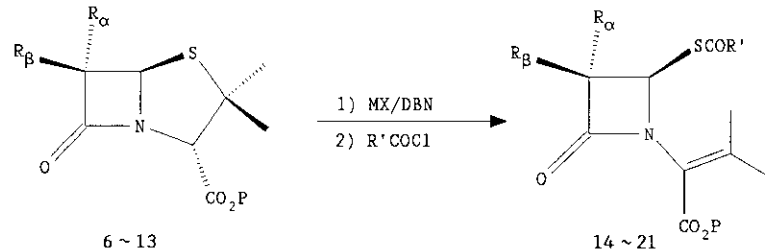
Substrate	MX	Time[2]	Substrate	MX	Time
1b	AgOAc	1 min	**1g**	AgOAc	3.5 h
1c	"	15 min	**1h**	PhHgCl	3 h
1d	"	45 min	**1i**	"	6.5 h
1e	"	1 h	**1a**	AgOAc	2 h
1f	"	2.3 h	"	PhHgCl	12 min

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 CH_2CCl_3 > CH_2OCOCH_3 > $CH_2CH=CH_2$ ≥ CH_2-C6H4-NO_2 > CH_2-C6H4-OCH_3 > $CH_2CH_2Si(CH_3)_3$ > $CH(C_6H_5)_2$ > $C(CH_3)_3$, 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 C_6 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 successfull 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 C_6-sidechain on the 1,2-cleavage/acylation of penicillanates



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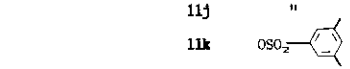
Penam Substrate				Ring-Opening/Acylation Conditions			4-Azetidinonyl-Thioester Product				
									Selected Spectroscopic Data		
#	R_α[1]	R_β[1]	P[1]	MX	Time[2,3] (h)	R'[1]	#	yield (%)	ir($CHCl_3$) ν_{max}(cm^{-1})	^{1}H nmr ($CDCl_3$) H-3	δ(J,Hz) H-4
6a	Br	(R)-CH(CH$_3$)OTBDMS	TCE	$AgNO_3$	2.5	CH_2OTBDPS	**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$_3$)OTMS	AOM	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$_3$)OTBDMS	TCE	PhHgCl	2	"	**15**	96	1765,1740,1695	3.60(dd,J=3,5.5)	5.97 (d,J=5.5)
8a	(S)-CH(CH$_3$)OTBDMS	Br	AOM	$AgNO_3$	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$_3$)OTBDMS	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_2O	5	"	"	49	"	"	"
9c	"	"	PMB	AgCl	4 (DMA)	$CH_2OCOCH_2CH_2CH_3$	**17c**	51	1755,1710	3.20 (dd,J=2,5.5)	5.22 (d,J=2)
9d	(R)-CH(CH$_3$)OTMS	"	AOM	"	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	$CH_2CH_2CH_3$	"	PMB	"	6	CH_2OCH_3	**18a**	33	1755,1705	3.19 (m)	5.36 (d,J=2)
10b	$CH_2CH_2OCOCH_3$	"	PMB	"	1	"	**18b**	72	1755,1725,1700 (sh)	3.27 (m)	5.41 (d,J=2.1)
10c	$CH_2CH_2OCO_2$PNB	"	"	"	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				
									Selected Spectroscopic Data		
#	R_α[1]	R_β[1]	P^1	MX	Time[2,3] (h)	R'	#	yield (%)	ir($CHCl_3$) $\nu_{max}(cm^{-1})$	^1H nmr ($CDCl_3$) H-3	δ(J,Hz) H-4
10d	$CH_2CH_2OTBDPS$	H	PNB	AgCl	2	CH_2OCH_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	1765,1735,1700	α:3.53(dd,J=5,15) ß:2.95(dd,J=2.5,15)	5.78 (m)
11b	"	"	BN	AgCl	2	CH_2Ph	**19b**	52	1753,1710,1690(sh)	α:3.46(dd,J=5.1,15.6) ß:2.93(dd,J=2.7,15.6)	5.65 (dd,J= 2.7,5.1)
11c	F	"	TCE	"	4	CH_2OCH_3	**19c**	40	1777,1734,1710	5.53(dd,J=2,54)	5.89(dd,J=2,11)
11d	Cl	"	PNB	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	"	PNB	PhHgCl	1	CH_2OPh	**19f**	76	1770,1715,1695	4.81 (d,J=2)	5.45 (d,J=2)
11g	OCO_2TCE	"	TCE	"	0.2	CH_3	**19g**	41	1786,1732,1705	5.82 (d,J=2)	5.68 (d,J=2.8)[4]
11h	$OCOCH_3$	"	PNB	"	0.5	CH_2OPh	**19h**	75	1784,1758,1725-1695	5.62 (2H,s)	
11i	$OCOCH_2OPh$	"	"	AgOAc	0.2	"	**19i**	39	1780,1720,1700(sh)	5.77(d,J=2)	5.68 (d,J=2)[4]
11j	"	"	AOM	AgCl	0.04	"	**19j**	63	1775,1740(sh),1695	5.80(d,J=2)	5.72 (d,J=2)[4]
11k		"	PNB	"	0.2	CH_2OCH_3	**19k**	51	1765,1740-1690(sh)	5.24(d,J=2)	5.69 (d,J=2)[4]
12a	H	$NHCOCH_2OPh$	TCE	PhHgCl	0.5	CH_3	**20a**	60	1775,1732,1698	5.32(dd,J=5,8)	6.11 (d,J=5)
12b	"	"	PNB	AgOAc	6	"	**20b**	78	1775,1730,1695		
12c	"	$NHCPh_3$	"	AgCl	3.5	"	**20c**	63	1760,1708	4.66(dd,J=4.5,8)	5.44 (d,J=4.5)
13	"	Phth	TCE	PhHgCl	4	"	**21**[5]	18	1775,1725,1700(sh)	6.32(d,J=5.5)	5.82 (d,J=5.5)

1) Abbreviations are as follows: TBDMS = tert-butyldimethylsilyl; TBDPS = tert-butyldiphenylsilyl; TMS = trimethylsilyl; TCE = trichloroethyl; AOM = acetoxymethyl; PNB = p-nitrobenzyl; PMB = p-methoxybenzyl; BN = benzyl; BZH = benzhydryl; Me = methyl; Phth = phtalimido.

2) Reaction time before quenching with R'COCl

3) General reaction conditions are as detailed in Footnote 1, Table 1, (CH_3CN as solvent) unless otherwise stated.

4) Attribution of the ^1H nmr signals due to H-3 and H-4 of the ß-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 C_3 or C_4 (azetidinone numbering) was ever observed, apart from the case of 6,6-dibromo (**1a-i**) and 6ß-phtalimido (**13**) substrates. The latter, under the conditions stated in Table 3, afforded a 1:4 mixture of "cis" (3R) thioester **21** and its C_3 epimer (3S). The increased acidity of the proton adjacent to the phatalimido group (and α to the ß-lactam carbonyl) facilitates its removal by DBN and thus accounts for the preferential formation of the less sterically congested trans arrangement on the ß-lactam ring. Substituting an acylamino or, even better, a tritylamino for the phtalimido group, avoided the C_3 epimerization to take place (Table 3; entries **12a-c**). Various degrees of epimerization at C_4 [leading in some cases to completely racemic thioester products] were uncovered[12] in the ring-opening reaction of 6,6-dibromopenicillanates (**1a-i**) by using (R)- and (S)-Mosher's acid chlorides[13] as the acylating agents. This fact was undetected at the time of our preliminary communication[1] 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 C_4-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-h] 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 acid[10] (DBPA) with pyridine (2.5 eq.) and $ClCOOCH_2CCl_3$ (2.0 eq.) in EtOAc (2 h, -10°C to room temperature, 93% yield), mp 86-88°C; ir (nujol) νmax 1800, 1760cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.56(3H,s), 1.67(3H,s), 4.68(1H,s), 4.80(2H,s), 5.83(1H,s). Anal. Calcd for $C_{10}H_{10}Br_2Cl_3NO_3S$: 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 $NaHCO_3$ and $BrCH_2OCOCH_3$ (2 eq. each) in DMF (5°C, 30 min, thence 20 h at room temperature, 86%), mp 83-84°C; ir (nujol) νmax 1780, 1750, 1740 cm^{-1} ; ^1H nmr ($CDCl_3$) 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 $C_{11}H_{13}Br_2NO_5S$: 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 NEt_3 and allyl bromide (1.5 eq. each) (0°C, overnight, 83%), oil; $[\alpha]_D$ + 186° (c 2.0, $CHCl_3$); ir ($CHCl_3$) 1790, 1735 cm^{-1}; ^1H nmr ($CDCl_3$) 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 NEt_3 and p-methoxybenzyl chloride (1.5 eq. each) in DMF (overnight,

75%), mp 90-91°C; ir (KBr) √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 $C_{16}H_{17}Br_2NO_4S$: 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) √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° (c 1.5, $CHCl_3$). Anal. Calcd for $C_{13}H_{21}Br_2NO_3SSi$: 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) √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 $C_{12}H_{17}Br_2NO_3S$: 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 ($CHCl_3$) √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 $C_{11}H_{13}Br_2NO_4S$: 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 ($CHCl_3$) √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 $C_{12}H_{12}Br_2Cl_3NO_4S$: 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 ($CHCl_3$) √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 $C_{13}H_{15}Br_2NO_6S$: 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 ($CHCl_3$) √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 $C_{13}H_{15}Br_2NO_4S$: 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 ($CHCl_3$) √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 $C_{17}H_{16}Br_2N_2O_6S$: 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 ($CHCl_3$) νmax 1778, 1700 cm^{-1}; ^1H nmr ($CDCl_3$) 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 ($CHCl_3$) νmax 1770, 1700 cm^{-1}; ^1H nmr ($CDCl_3$) 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 ($CHCl_3$) νmax 1790, 1717 cm^{-1}; ^1H nmr ($CDCl_3$) 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) νmax 1792, 1780, 1710, 1660 cm^{-1}; ^1H nmr ($CDCl_3$) 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 $C_{14}H_{19}Br_2NO_4S$: 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 ($CHCl_3$) νmax 1780, 1730 cm^{-1}; ^1H nmr($CDCl_3$) δ 2.01(3H,s), 2.33(3H,s), 3.80(3H,s), 5.63(1H,s); foam. Anal. Calcd for $C_{18}H_{20}Br_4N_2O_6S_2$: 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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