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Application of lanthanide catalysis in the penicillin to cephalosporin conversion

Anthony G. M. Barrett,[a,*] D. Christopher Braddock,[a] Robin D. G. Cooper[b] and Julian P. Henschke[a]

[a]*Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, UK*
[b]*Cooper Consulting Inc, 6740 Dover Road, Indianapolis, IN 46220, USA*

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Abstract—*seco*-Penicillin sulfinyl carboxylates and chlorides were cyclized to produce the corresponding 3-methylenecepham systems, intermediates for cephalosporin antibiotic manufacture, either under thermal or ytterbium(III) triflate catalyzed conditions.

1. Introduction

Lanthanide(III) triflates and related species have enjoyed recent attention as catalysts for a wide range of reactions in organic synthesis.[1,2] The interest stems from their apparent ability to function as strong Lewis acids even in Lewis basic solvents such as tetrahydrofuran and water, and by their relatively high turnover numbers compared to traditional Lewis acids.[3] For instance, ytterbium(III) triflate was found to catalyze the Mukaiyama aldol reaction of silyl ketene acetals with aqueous formaldehyde solution.[4] In the latter category, these compounds have been found to be effective catalysts (10 mol%) for Friedel–Crafts acylation reactions[5,6] where typically 'classical' Lewis acid catalysts must be used in at least stoichiometric quantities.[7] Notably, in many cases the lanthanide(III) triflate may be recovered from a reaction mixture by extraction into an aqueous phase and recycled by evaporation.

We have recently reported several novel catalytic applications of lanthanide(III) triflates including atom economic electrophilic nitration of arenes in the absence of sulfuric acid,[8] oxidation of benzylic alcohols with nitric acid,[9] the preparation of resorcinarenes,[10] and alcohol acetylation using acetic acid.[11] For the resorcinarene[10] and nitration chemistry[9,12,13] it has been demonstrated that the lanthanide(III) triflates operate via Lewis assisted enhancement of Brønsted acidity.[14] Thus, lanthanide(III) triflates may function not only as mild Lewis acids but also as a convenient and recyclable source of the strong Brønsted acid triflic acid.

Both penicillins and cephalosporins have found widespread use in the treatment of bacterial infections.[15] The primary drawbacks associated with several important cephalosporin antibiotics relate to the difficulty and expense of their synthetic production from penicillin precursors. For example, the manufacture of cefaclor **4** and related cephalosporin antibiotics, involves the cyclization of the *seco*-penicillin sulfinyl chloride **2** into the corresponding 3-methylenecepham β-sulfoxide **3** using stoichiometric quantities of tin(IV) chloride (Scheme 1). Clearly this transformation is neither optimal from the viewpoint of atom economy nor from the potential for environmental risk. In this paper we wish to report our studies of ytterbium(III) triflate catalysis for the cyclization of sulfinyl chloride **2** and related transformations. We additionally report the synthesis and characterization of *seco*-penicillin sulfinyl carboxylates.

2. Results and discussion

2.1. Synthesis of *seco*-penicillin sulfinyl carboxylates

Given the highly oxophilic, rather than halophilic, nature of lanthanide triflates we proposed to prepare novel analogues of sulfinyl chloride **2** that contained an oxygen based leaving group. By analogy to Friedel–Crafts acylation of olefins and arenes with carboxylic anhydrides we chose to investigate the hitherto unknown *seco*-penicillin sulfinyl carboxylates as functional equivalents of the currently used sulfinyl chloride. Sulfinyl carboxylates have received little attention in the literature, probably as a result of their instability. In fact, Oae et al.[16] has shown that simple sulfinyl carboxylates prepared from methanesulfinyl chloride and silver acetate or benzoate could only be studied in solution, and decomposed through disproportionation upon evaporation of the solvent. We hoped to utilize

Keywords: ytterbium(III) triflate; cephalosporin; antibiotics; sulfinyl carboxylate.

* Corresponding author. Tel.: +44-207-594-5767; fax: +44-207-594-5805; e-mail: m.sahrle@ic.ac.uk

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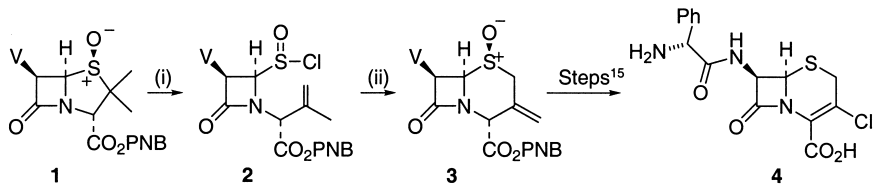
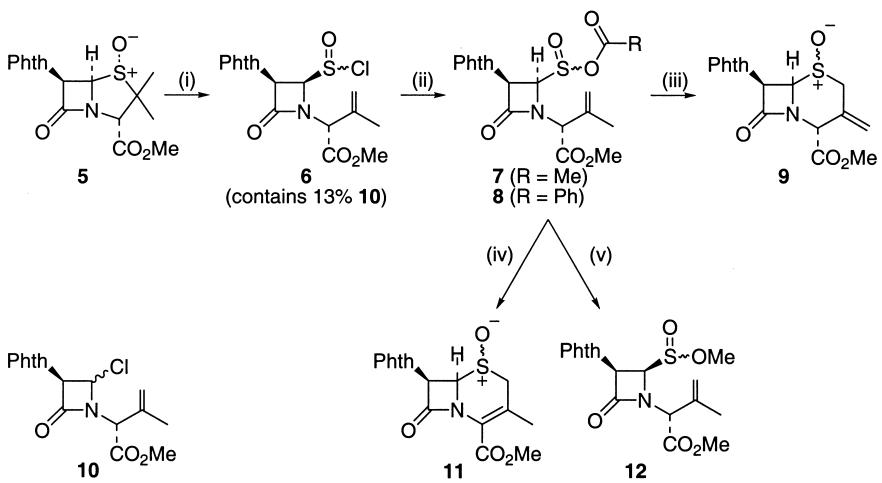


Scheme 1. *Reagents and conditions*: (i) PhMe, Δ, *N*-chlorophthalimide; (ii) PhMe, $SnCl_4$; V=$PhOCH_2CONH$.

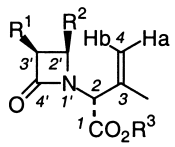
this instability in the development of a mild protocol for the conversion of *seco*-penicillin sulfinyl carboxylates into 3-methylenecephams.

We began our investigation with the phthalimido penicillin α-sulfoxide **5**[17,18] since its derivatives are more robust[19] than the corresponding penicillin V systems. Chlorination of sulfoxide **5** using *N*-chlorosuccinimide in carbon tetrachloride (Scheme 2) gave the *seco*-penicillin sulfinyl chloride **6** (87% of the mixture) along with an inseparable mixture of chloroazetidinone **10**[20] (13% as a mixture of epimers). We were initially encouraged in a ^1H NMR experiment to observe that reaction of sulfinyl chloride **6**,[21,22] with silver acetate (1.1 equivalents) at −20°C in deuterochloroform provided a new, albeit impure, component, that consisted of two diastereoisomers with the characteristic *cis*-azetidinone[23] resonances in the ^1H NMR spectrum. These were assigned as the two sulfur centered diastereo isomers (assigned **a** and **b**) of **7** on the basis of their spectral data (Table 1) and chemical reactivity (vide infra). On a preparative scale, the same transformation was achieved by the use of silver acetate (1 equivalent) in carbon tetrachloride at reflux to give sulfinyl acetate as a 1:1 mixture of diastereoisomers epimeric at sulfur (85%).



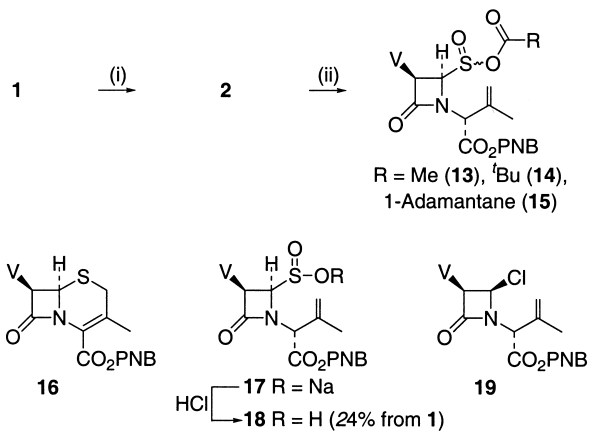
Scheme 2. *Reagents and conditions*: (i) NCS, CCl_4; (ii) AgOAc or AgOBz, CCl_4, Δ; (iii) 10 mol% $[Yb(OH_2)_9](OTf)_3$, $MeNO_2$, 20 °C; (iv) Et_3N, CH_2Cl_2, 20°C; (v) MeOH, 20°C. Phth=phthalimido.

Table 1. ^1H NMR signals from sulfinyl carboxylates **7**, **8**, **13**, **14** and **15**



Compound	R^1	R^2	R^3	$\delta_{H3'}$	$\delta_{H2'}$	δ_{H2}	$\delta_{H4a,b}$	$\delta_{H(C3\text{-}Me)}$
7a	Phth	SO_2Ac	Me	5.83 (d)	5.42 (d)	4.98 (s)[a]	5.08 (s),[a] 5.12[a] (s)	2.00[a] (s)
7b	Phth	SO_2Ac	Me	5.76 (d)	5.39 (d)	5.07 (s)[a]	5.24 (d),[a] 5.18[a] (s)	2.03[a] (s)
8a	Phth	SO_2Bz	Me	5.94 (d)	5.85 (d)	4.63 (s)	4.91 (m), 5.17 (s)	2.02 (s)
8b	Phth	SO_2Bz	Me	5.88 (d)	5.59 (d)	5.11 (s)	5.29 (d), 5.15 (s)	2.05 (s)
13a	V	SO_2Ac	PNB	6.11 (dd)	5.22 (d)	4.97 (s)	5.24 (q), 5.08 (s)	1.96 (bs)
13b	V	SO_2Ac	PNB	5.73 (dd)	5.13 (d)	4.92 (s)[b]	5.18 (q), –[c]	1.89 (bs)
14a	V	SO_2Pv	PNB	6.22 (dd)	5.24 (d)	4.98 (s)	5.26 (m), 5.09 (s)	1.97 (s)
14b	V	SO_2Pv	PNB	5.74 (dd)	5.08 (d)	–[c]	–[c]	1.88 (s)
15a	V	SO_2Adm	PNB	6.23 (dd)	5.23 (d)	4.99 (s)	5.26 (m), 5.10 (s)	–
15b	V	SO_2Adm	PNB	5.76 (dd)	5.07 (d)	–[c]	–[c]	–[c]

$CDCl_3$, 270 MHz; Phth=Phthalimido; V=$PhOCH_2CONH$; Pv=CO^tBu; Adm=1-adamantylcarbonyl.
[a] Interchangeable between **7a** and **7b**.
[b] Tentative assignment.
[c] Obscured by other resonances.



Scheme 3. *Reagents and conditions*: (i) NCS, PhMe, Δ; (ii) RCO_2M (Na, K, Cs, or Ag), PhMe, THF or PhMe, Et_2O, 20°C.

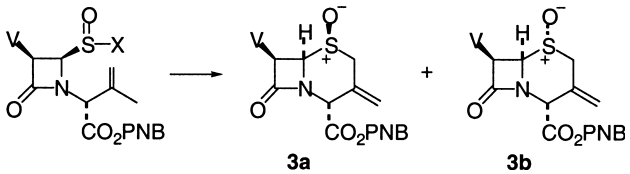
Pleasingly, sulfinyl acetate **7** was found to be much more stable than other sulfinyl carboxylates reported[16] and did not decompose during aqueous work-up. However, we were unable to isolate the sulfinyl acetate **7** by normal phase chromatography as it rapidly decomposed and the presence of impurities precluded its microanalysis. Although the sulfinyl acetate **7** was found to be considerably more water tolerant than sulfinyl chloride **6**, it reacted in an identical manner to the chloride **6** when allowed to react with triethylamine or methanol, providing the known 3-cephem **11**[24] and methyl sulfinate **12**, respectively, thereby behaving in a manner fully consistent with the proposed assignment of structure as the sulfinyl acetate **7**.

Sulfinyl acetate **7** underwent cyclization to furnish the desired phthalimido 3-methylenecepham sulphoxide **9** in the presence of hydrated or anhydrous ytterbium(III) triflate in tetrahydrofuran, dichloromethane, 2,4-pentanedione, acetonitrile, methyl acetate, nitromethane or nitroethane. The best conditions for formation of sulfoxide **9** from acetate **7** were the use of ytterbium(III) triflate nonahydrate (10 mol%) in nitromethane at room temperature giving a 73% NMR yield of cepham **9**. Similarly, *seco*-penicillin sulfinyl benzoate **8**, derived from sulfinyl chloride **6** using silver benzoate, also underwent ytterbium(III) triflate catalyzed cyclization in nitromethane providing the 3-methylenecepham **9** in 50% yield as judged by NMR spectroscopy.

2.2. Penicillin V system

Having successfully realized our methodology in the model system, we began investigating its application in the exact penicillin V system used in cefaclor **4** manufacture (Scheme 3). The requisite sulfinyl chloride **2**,[21,22] which was used immediately as a crude solution in toluene, was prepared from penicillin V sulfoxide **1**.[25] Efforts to prepare the penicillin V derived sulfinyl acetate **13** from **2** utilized silver, sodium, potassium or cesium acetate. In contrast to the finding in the model system, sulfinyl acetate **13** was more successfully prepared using sodium acetate than with silver acetate resulting in the formation of acetate **13** in 93% purity containing the known[26] *cis*-chloroazetidinone **19** (2%) and an unidentified azetidinone impurity (ca. 4%). However, the product was highly sensitive and the reaction failed with trace amounts of moisture present, nor could **13**

Table 2. One pot conversion of *seco*-penicillin sulfinyl carboxylates **13** and **14** and chloride **2** into 3-methylenecepham **3**



Entry	X	Time (h)	Solvent	Temperature (°C)	% Yield[a] (**3a**, **3b**)	Catalyst (10 mol%)	Additive
1	OAc	4	CH_2Cl_2	Reflux	–, – (1:1)[b]	None	–
2	OAc	4.5	PhMe-THF	Reflux	–, – (1:2.7)[b]	None	–
3	OAc	1	None	70	16, 7 (1:0.1)	None	–
4	OAc	0.5	None	125	21, 6 (1:0.2)	None	–
5	OAc	120	PhMe	20	–, – (0:1)[b]	None	–
6	OPv	168	PhMe-Et_2O	20	14, 27	None	–
7	OPv	47	None	75	31, 10	None	–
8	OPv	23	$MeNO_2$	20	33, 10	$Yb(OTf)_3$	–
9	OPv	92	$MeNO_2$	20	20[b]	None	–
10	Cl	96	PhMe	20	–	$Yb(OTf)_3$	NaOPv[c]
11	Cl	504	PhMe	20	0	$Yb(OTf)_3$	–
12	Cl	17	PhMe	70	0	$Yb(OTf)_3$	–
13	Cl	40	$MeNO_2$	20	49, 4	$Yb(OTf)_3$	NaOPv[c]
14	Cl	117	$MeNO_2$	20	Trace	None	NaOPv[c]
15	Cl	21	$MeNO_2$	20	46, –[d]	$Yb(OTf)_3$	–
16	Cl	22.5	MeCN	20	30, –[d]	$Yb(OTf)_3$	–
17	Cl	22	$MeNO_2$	20	48[e]	$Yb(OTf)_3$	–

Pv=CO^{t}Bu; V=$PhOCH_2CONH$.
[a] Isolated yields, based on penicillin V sulfoxide **1**. Numbers in parentheses are ^{1}H NMR determined ratio of **3**:**16**.
[b] Products not isolated. Yield/ratio determined by ^{1}H NMR only.
[c] 1 Equivalent of fused material.
[d] Not isolated.
[e] Product precipitated as 87:13 mixture of **3a** and succinimide.

be isolated by chromatography. As before, the sulfinyl acetate **13** was formed as sulfur epimers with one diastereoisomer predominating (1.0:0.2).

Sulfinyl acetate **13** underwent spontaneous cyclization to produce the desired 3-methylenecepham β-sulfoxide **3a** either by heating the neat crude acetate **13** in vacuo or in a range of solvents (Table 2, entries 1–5). The epimeric sulfoxide **3b** was also generated along with varying quantities of 3-cephem **16**[27] (and numerous side products). Despite some promise the instability and difficulty in preparation of the sulfinyl acetate **13** and the low yield of cepham **3** was only modest (30% based on **1**) and therefore we sought to elaborate more stable analogues.

The sterically hindered sulfinyl pivaloate **14** and sulfinyl 1-adamantanecarboxylate **15** were also prepared by the action of sodium pivolate and sodium 1-adamantanecarboxylate on the sulfinyl chloride **2** respectively (Scheme 3). The pivaloate **14** proved to be easier to handle, more stable to heat, water and mild acid than the corresponding acetate **13**. The sulfinyl 1-adamantanecarboxylate **15** was obtained in comparable yield and, since its cyclization did not proceed in superior yield to the pivaloate **14**, was not investigated further.

In the preparation of sulfinyl pivaloate **14** the ^{1}H NMR spectrum indicated that it was formed in ca. 75% yield (internal standard) from the sulfinyl chloride **2** as a mixture of diastereoisomers (ca. 2–4:1.0) epimeric at sulfur. Pivalic anhydride was also found to be present in the crude mixture, probably formed by nucleophilic attack at the pivaloate carbonyl of sulfinyl pivaloate **14** by sodium pivaloate. In support of this we note that a 24% yield of sulfinic acid **18** was isolated from the reaction precipitate following acidification and extraction. It is expected that this mode of reactivity also occurred in the formation of the sulfinyl acetate **13**, partially accounting for the low yields of the desired sulfoxides **3** in the subsequent cyclization step.

Pivaloate **14** also underwent cyclization to the 3-methylenecepham sulfoxides **3a** and **3b** either in solution or by heating in vacuo (Table 2, entries 6, 7) in improved yield (41% isolated yield) compared to the acetate **13**, albeit with extended reaction times. Moreover, under the influence of catalytic quantities of ytterbium(III) triflate (10 mol%) in nitromethane solution the reaction could be conducted at room temperature in 24 h to give comparable conversion (entry 8). In an effort to improve the procedure, we believed that the in situ decomposition leading to pivalic anhydride could be minimized by a one-pot preparation and cyclization protocol. Sulfinyl chloride **2** did not undergo cyclization in toluene in the presence of ytterbium(III) triflate (10 mol%) with added sodium pivaloate (entry 10). When, however, the reaction was conducted with sodium pivaloate (1 equivalent) in nitromethane a 49% isolated yield of 3-methylenecepham β-sulfoxide **3a** and a 4% yield of the α-sulfoxide **3b** was obtained (entry 13). Interestingly the ratio of the β- to α-sulfoxides was much higher than seen in previous cyclization reactions. A small amount of pivalic anhydride (^{1}H NMR spectroscopy) in the product mixture suggested the intermediacy of the pivaloate **14**. In the absence of the lanthanide catalyst, only trace amounts of the product was detected (entry 14). To our surprise sulfinyl chloride **2** itself underwent direct cyclization in nitromethane in the presence of ytterbium(III) triflate (10 mol%) to furnish 3-methylenecepham β-sulfoxide **3a** in 46% yield *in the absence* of sodium pivaloate (entry 15). This was unexpected because sulfinyl chloride **2** did not undergo cyclization in the presence of ytterbium(III) triflate (10 mol%) at room temperature (entry 11) or at 70°C (entry 12) in toluene. This result meant that we could *directly cyclize the sulfinyl chloride **2** to the 3-methylenecepham sulfoxide **3a*** without the need for sulfinyl carboxylates *making the process now competitive with Kukolja's tin(IV) tetrachloride methodology*, with the significant advantage that only catalytic quantities of the Lewis acid are required. As a comparison, it is worth noting that in Kukolja's[21,28] conversion of penicillin V sulfoxide **1** (12 mmol scale) to 3-methylenecepham β-sulfoxide **3a** using the industrial protocol, a 36% overall yield was obtained. Previously we have shown that acidic solvents such as nitromethane, acetic acid and acetonitrile combine with metal triflates to produce strong Brønsted acid(s) which can promote catalysis. It might be speculated that the primary form of catalysis in this reaction is Brønsted acid,[10] rather than Lewis acid. Consistent with this acetonitrile (entry 16) was also a suitable solvent for cyclization from sulfinyl chloride **2** but toluene, tetrahydrofuran, *N*,*N*-dimethylacetamide and dichloromethane were not. Attempts to induce the cyclization with reduced quantities of nitromethane in the reaction medium using toluene as a co-solvent were unsuccessful.

Finally, we briefly examined the possibility of removing chromatographic purification from the process. When the crude product mixture (after cyclization according to entry 17) was allowed to precipitate from ethyl acetate pure 3-methylenecepham β-sulfoxide **3a** (48%) free from all other impurities, except succinimide, (87:13, respectively) was obtained. A further 20% (^{1}H NMR spectroscopy) of 3-methylenecepham sulfoxide **3a** remained in the filtrate.

In conclusion, we have shown that hitherto unreported azetidinone sulfinyl carboxylates undergo cyclization into 3-methylenecepham sulfoxides under a range of catalyzed or non-catalyzed conditions. Moreover, we discovered that sulfinyl chloride **2** itself could be directly converted into the desired product in nitromethane or acetonitrile in the presence of ytterbium(III) triflate catalyst (10 mol%). We believe that the lack of cyclization of sulfinyl chloride **2** in solvents (toluene, tetrahydrofuran, dichloromethane and DMAC) other than those previously[10] identified (nitromethane and acetonitrile) reinforces our findings that lanthanide(III) and other metal triflate salts react with weakly acidic solvents to produce strong Brønsted acids which can be responsible for the primary mode of catalysis.

3. Experimental

3.1. General

All reactions were conducted under a dry inert atmosphere (argon or nitrogen). All glassware was dried in an oven (ca. 150°C), or flame dried, and cooled under a dry inert

atmosphere before use. Solvents and reagents were purified and dried as described by Perrin and Armarego.[29] Carbon tetrachloride was distilled from P_2O_5 and stored over 4 Å molecular sieves under a dry inert atmosphere. Silica Gel 60 (Merck) was used for column chromatography (eluants are given in parentheses). Anhydrous sodium acetate is hygroscopic and was fused in situ under vacuum (ca. 0.1 mmHg). Sodium pivaloate was purchased from Aldrich as a hydrate (level of hydration not specified) and was fused in situ under vacuum (ca. 0.1 mmHg). ESI mass spectra were recorded in the positive ion mode. Anhydrous $Yb(OTf)_3$ was prepared by drying the nonahydrate (Aldrich) in vacuo at 190°C for 24 h, cooled (Ar) and used immediately without exposure to the atmosphere. For determination of the yields in the conversion of **7** the internal standard method was used. A reference mixture of **9** and the internal standard 1,3,5-tri-*tert*-butylbenzene was prepared for calibration. The integral was measured for the trimethyl signal (δ 1.34 in $CDCl_3$) of the internal standard and was compared to those of both azetidinone signals (δ 5.95 and 4.90) summed together for the (*R*)-**9**.

3.1.1. (2*R*)-Methyl 2-[(2*R*,3*R*)-2-acetoxysulfinyl-4-oxo-3-phthalimido-1-azetidinyl]-3-methyl-3-butenoate (7). AgOAc (110 mg, 0.66 mmol) was added to **6** (0.66 mmol) in CCl_4 (14 mL) prepared as described by Kukolja.[21,22] The mixture was stirred under reflux for 40 min, and the mixture was diluted with $CHCl_3$ (20 mL) and filtered. The solid residue was washed with $CHCl_3$ (10 mL) and was filtered. The combined $CHCl_3$ extracts were washed with H_2O (5 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated to give a white foam (295 mg). ^{1}H NMR spectroscopy indicated that the product mixture contained sulfinyl acetate **7** (purity 85%) as a 1:1 mixture of diastereoisomers: IR (thin film, KBr) 1792, 1778, 1725, 1387 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91 (s, 3H, OAc), 2.00 (s, 3H, C3-*Me*), 2.03 (s, 3H, C3-*Me*), 2.12 (s, 3H, OAc), 3.83 (s, 3H, CO_2Me), 3.85 (s, 3H, CO_2Me), 4.98 (s, 1H), 5.07 (s, 1H), 5.08 (s, 1H), 5.12 (s, 1H), 5.18 (s, 1H), 5.24 (d, *J*=1.3 Hz, 1H), 5.39 (d, *J*=5.3 Hz, 1H, **7b**-H2′), 5.42 (s, *J*=5.0 Hz, 1H, **7a**-H2′), 5.76 (d, *J*=5.0 Hz, 1H, **7b**-H3′), 5.83 (d, *J*=5.3 Hz, 1H, **7a**-H3′), 7.78 (m, Phth), 7.88 (m, Phth); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.8, 21.0, 21.1, 52.6, 52.7, 55.8, 56.5, 58.9, 60.5, 75.3, 79.2, 116.9, 118.7, 123.9, 131.0, 131.5, 134.6, 135.0, 137.3, 138.9, 163.6, 163.8, 166.3, 166.5, 167.5, 167.8, 168.5, 168.6; CIMS *m/z* 394 [93%, $(M+NH_4-58)^+$], 377 [34, $(M+H-58)^+$], 376 [94, $(M-58)^+$], 359 (48), 346 (51), 329 (35), 130 (100), 124 (47), 112 (91); ESIMS (MeCN) *m/z* 473 [40%, $(M+K)^+$], 457 [100, $(M+Na)^+$], 435 [60, $(M+H)^+$]; ESIMS (MeCN, CsI) 567 [100%, $(M+Cs)^+$].

3.1.2. (2*R*)-Methyl 2-[(2*R*,3*R*)-2-benzoyloxysulfinyl-4-oxo-3-phthalimido-1-azetidinyl]-3-methyl-3-butenoate (8). AgOBz (16 mg, 0.07 mmol) was added to **6** (0.07 mmol) in CCl_4 (1.4 mL) prepared as described by Kukolja.[21,22] The mixture was stirred under reflux for 40 min, and the mixture was diluted with $CHCl_3$ (4 mL), dried ($MgSO_4$), filtered and evaporated to furnish crude **8** (35 mg, 0.07 mmol, 100%) as a colorless oil. ^{1}H NMR spectroscopy revealed sulfinyl benzoate **8** was obtained as a mixture of two diastereoisomers (1.0:1.5 ratio): IR (thin film, KBr) 1788, 1781, 1725, 1388 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.02 (s, **8a**-C3-*Me*), 2.05 (s, **8b**-C3-*Me*), 3.79 (s, **8a**-CO_2Me), 3.87 (s, **8b**-CO_2Me), 4.63 (s, **8a**-H2), 4.91 (m, **8a**-H4), 5.11 (s, **8b**-H2), 5.15 (s, **8b**-H4), 5.17 (s, **8a**-H4), 5.29 (d, *J*=1.5 Hz, **8b**-H4), 5.59 (d, *J*=5.5 Hz, **8b**-H2′), 5.85 (d, *J*=5.2 Hz, **8a**-H2′), 5.88 (d, *J*=5.5 Hz, **8b**-H3′), 5. 94 (d, *J*=5.2 Hz, **8a**-H3′), 7.31–7.71 (m, Ph), 7.76 (m, Phth), 7.89 (m, Phth), 8.03–8.12 (m, Ph); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.0, 52.5, 52.8, 55.8, 56.4, 58.5, 60.4, 75.8, 80.7, 116.9, 118.9, 123.7, 124.0, 127.2, 128.3, 128.5, 128.6, 130.0, 130.1, 130.5, 130.9, 131.5, 133.5, 134.6, 138.7, 163.6, 164.0, 164.1, 168.8, 177.2. ESIMS (MeCN, trace AcOH) *m/z* 535 [20%, $(M+K)^+$], 519 [100, $(M+Na)^+$], 514 [60, $(M+NH_4)^+$]; ESIMS (MeCN, CsI) *m/z* 629 [100%, $(M+Cs)^+$].

3.1.3. (4*R*,6*R*,7*R*)-Methyl 7-phthalimido-3-methylene-cepham-4-carboxylate 1-oxide (9a and 9b).[21] *General procedure for Yb(OTf)$_3$ catalyzed cyclization of sulphinyl acetate 7.* Solutions of **7** (15 mg, ca. 35 μmol) in anhydrous THF, CH_2Cl_2, MeCN, Ac_2CH_2, MeOAc, $MeNO_2$ or $EtNO_2$ (500 μL) were stirred at room temperature in the presence of anhydrous $Yb(OTf)_3$ (2 mg, 3.5 μmol; for runs in THF, CH_2Cl_2, MeCN, MeOAc, $MeNO_2$) or $[Yb(OH_2)_9](OTf)_3$ (2.7 mg, 3.5 μmol; for runs in Ac_2CH_2, $MeNO_2$ or $EtNO_2$). The mixtures were diluted with $CHCl_3$ (1 mL) and washed with brine (0.5 mL), dried ($MgSO_4$), filtered and evaporated. ^{1}H NMR spectroscopy was used to determine the efficacy of the reaction using the internal standard method.

Yb(OTf)$_3$ catalyzed cyclization of sulphinyl acetate 7 in $MeNO_2$. $[Yb(OH_2)_9](OTf)_3$ (2.7 mg, 3.5 μmol, 10 mol%) was added to **7** (15 mg, ca. 35 μmol) in $MeNO_2$ (500 μL). The mixture was stirred at room temperature for 5 h, and was diluted with $CHCl_3$ (1.5 mL) and washed with brine (0.2 mL). The aqueous washings were extracted with $CHCl_3$ (0.5 mL) and the combined $CHCl_3$ extracts were dried ($MgSO_4$), filtered and evaporated to provide **9** (12 mg). Tri-*tert*-butylbenzene (8.6 mg, 0.035 mmol) was added to the product and the mixture was dissolved in $CDCl_3$ (500 μL) and analysed by ^{1}H NMR spectroscopy: this indicated the mixture contained cepham **9** (73%).

3.1.4. (2*R*)-4-Nitrobenzyl 2-[(2*R*,3*R*)-2-acetoxysulfinyl-4-oxo-3-phenoxyacetamido-1-azetidinyl]-3-methyl-3-butenoate (13). A mixture of fused NaOAc (16 mg, 0.19 mmol) and THF (3 mL) was sonicated for 0.5 h to which a PhMe (70 mL) solution of **2** (0.20 mmol), prepared as described by Kukolja,[21,22] was added. The mixture was stirred for 18 h, filtered through a 0.45 μm PTFE syringe filter and evaporated under a stream of inert gas. ^{1}H NMR spectroscopy indicated the residue contained sulfinyl acetate **13** as two diastereoisomers, epimeric at sulfur, in a 1.0:0.2 ratio. The sulfinyl acetate **13** was too unstable to obtain a ^{13}C NMR spectrum: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.89 (bs, **13b**-C3-*Me*), 1.96 (bs, **13a**-C3-*Me*), 2.01 (s, **13a**-OCO*Me*), 2.13 (s, **13b**-OCO*Me*), 4.40 (s), 4.47 (d, *J*=15.0 Hz, **13a**-PhOCH_2), 4.53 (s), 4.59 (d, *J*=15.0 Hz, **13a**-PhOCH_2), 4.64 (s), 4.72 (s), 4.92 (s, **13b**-H2), 4.97 (s, **13a**-H2), 5.08 (s, **13a**-H4b), 5.13 (d, *J*=5.1 Hz, **13b**-H2′), 5.18 (q, *J*=1.5 Hz, **13b**-H4a), 5.22 (d, *J*=4.6 Hz, **13a**-H2′), 5.24 (q, *J*=1.5 Hz, **13a**-H4a), 5.29 (d, *J*=9.0 Hz, **13a**-CO_2CH_2), 5.34 (d, *J*=9.2 Hz, **13a**-CO_2CH_2), 5.73 (dd, *J*=4.9, 8.3 Hz, **13b**-H3′), 6.11 (dd, *J*=4.9, 10.6 Hz, **13a**-H3′), 6.86–7.08 (m, Ph), 7.13–7.36 (m, Ph), 7.47–7.60 (m, $ArNO_2$), 8.09 (d,

J=10.40 Hz, N*H*), 8.19–8.28 (m, $ArNO_2$); ESIMS (MeCN, NaCl) *m/z* 582.5; ESIMS (MeCN, KCl) *m/z* 598.4; ESIMS (MeCN, CsCl) *m/z* 692.4.

3.1.5. (2*R*)-4-Nitrobenzyl 2-[(2*R*,3*R*)-2-(*tert*-butylcarbonyloxy)sulfinyl-4-oxo-3-phenoxyacetamido-1-azetidinyl]-3-methyl-3-butenoate (14). A PhMe (70 mL) solution of **2** (1.99 mmol), prepared as described by Kukolja,[21,22] was added to a sonicated mixture of fused $^tBuCO_2Na$ (283 mg of $^tBuCO_2Na.xH_2O$; x not specified, 2 mmol) in Et_2O (20 mL) and the mixture was stirred for 22 h. The precipitate was allowed to settle, the liquid layer was filtered through a 0.45 μm PTFE syringe filter and was evaporated using short path distillation at room temperature, without exposure of the product to the atmosphere, giving crude sulfinyl pivaloate **14** as a yellow foam: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.11 (s, 9H, **14a**-C*Me*$_3$), 1.21 (s, **14b**-C*Me*$_3$), 1.88 (bs, **14b**-C3-*Me*), 1.97 (bs, **14a**-C3-*Me*), 4.40 (d, J=14.8 Hz, **14a**-PhOCH_2), 4.57 (d, J=15.0 Hz, **14a**-PhOCH_2), 4.88 (s), 4.98 (s, **14a**-H2), 5.08 (d, J=4.9 Hz, **14b**-H2′), 5.09 (s, **14a**-H4b), 5.24 (d, J=4.9 Hz, **14a**-H2′), 5.25 (d, J=12.9 Hz, **14a**-CO_2CH_2), 5.26 (q, J=1.5 Hz, **14a**-H4a), 5.34 (d, J=12.9 Hz, **14a**-CO_2CH_2), 5.74 (obscured dd, **14b**-H3′), 6.22 (dd, J=4.6, 10.6 Hz, **14a**-H3′), 6.86–7.02 (m, Ph), 7.15–7.36 (m, Ph), 7.52 (m, $ArNO_2$), 8.23 (m, $ArNO_2$); ^{13}C NMR ($CDCl_3$, 67.5 Hz) δ 21.7, 26.34, 26.5, 39.3, 58.0, 58.2, 66.0, 66.9, 73.6, 114.7, 119.0, 122.1, 123.8, 128.7, 129.6, 138.3, 141.3, 147.8, 156.7, 166.5, 167.9, 168.3, 175.7. ESIMS (MeCN, KCl) 640.0 [29% $(M+K)^+$], 320.4 (34), 304.4 (44), 124.3 (53), 108.3 (100). The precipitate formed during the reaction was treated with a mixture of $CHCl_3$ (20 mL) and 1 M HCl (8 mL) and was vigorously stirred for 10 min. The $CHCl_3$ was separated, washed with H_2O and brine, dried ($MgSO_4$), evaporated and filtered to give sulfinic acid **18**[26] (246 mg, 24%) as yellow foam with a ^1H NMR spectrum identical with authentic material.

3.1.6. (2*R*)-4-Nitrobenzyl 2-[(2*R*,3*R*)-2-(1-adamantylcarbonyloxy)sulfinyl-4-oxo-3-phenoxyacetamido-1-azetidinyl]-3-methyl-3-butenoate (15). NaH (23 mg of 60% dispersion, 0.60 mmol) was added to 1-adamantane carboxylic acid (108 mg, 0.60 mmol) in dry THF (6 mL) at 0°C. After stirring for 10 min, the mixture was allowed to warm up to room temperature and was stirred for 1 h. Chloride **2**[21,22] (0.60 mmol) in PhMe (21 mL) was added and the mixture was stirred for 25 h. The precipitate was allowed to settle and the product mixture was filtered through a 0.45 μm PTFE syringe filter and evaporated under a stream of dry nitrogen: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.72 (bm), 1.93 (bm), 2.03 (bm), 4.43 (d, J=14.8 Hz, **15a**-PhOCH_2), 4.60 (d, J=14.8 Hz, **15a**-PhOCH_2), 4.89 (s), 4.99 (s, **15a**-H2), 5.07 (d, J=4.9 Hz, **15b**-H2′), 5.10 (s, **15a**-H4b), 5.23 (d, J=4.6 Hz, **15a**-H2′), 5.26 (q, J=1.6 Hz, **15a**-H4a), 5.28 (obscured d, **15a**-CO_2CH_2), 5.35 (d, J=12.9 Hz, **15a**-CO_2CH_2), 5.76 (dd, J=5.0, 8.7 Hz, **15b**-H3′), 6.23 (dd, J=4.7, 10.7 Hz, **15a**-H3′), 6.86–7.05 (m, Ph), 7.14–7.35 (m, Ph), 7.52 (m, $ArNO_2$), 8.24 (m, $ArNO_2$); ^{13}C NMR ($CDCl_3$, 67.5 Hz) δ 21.4, 27.1, 35.6, 41.1, 58.0, 65.9, 66.8, 73.5, 114.6, 118.8, 122.0, 123.6, 128.6, 129.4, 138.1, 141.3, 147.6, 156.7, 166.4, 167.9, 168.1, ca. 182.

3.1.7. (4*R*,6*R*,7*R*)-4-Nitrobenzyl 3-methylene-7-phenoxyacetamidocepham-4-carboxylate-1-oxide (3a[21] and 3b[30]). *Uncatalyzed cyclization of sulfinyl pivaloate **14**.* A crude solution of **14** (2 mmol) in PhMe (70 mL) and Et_2O (20 mL) was stirred at room temperature for 7 days. The solvent mixture was evaporated and the product chromatographed (SiO_2, EtOAc:CH_2Cl_2 1:4) to provide **3a** (140 mg, 14%) and **3b** (265 mg, 27%). These compounds showed the following data: **3a**: R_f 0.15 (EtOAc:$CHCl_3$ 1:4); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.56 (1H, d, J=13.9 Hz, H2), 3.75 (1H, d, J=14.1 Hz, H2), 4.54 (2H, s, PhOCH_2), 4.90 (1H, d, J=4.6 Hz, H6), 5.27 (2H, s, CO_2CH_2), 5.31 (1H, s, H4), 5.48 (1H, d, J=1.6 Hz, C3=CH_2), 5.78 (1H, s, C3=CH_2), 6.03 (1H, dd, J=4.6, 10.6 Hz, H7), 6.90–7.05 (3H, m, Ph), 7.25–7.33 (2H, m, Ph), 7.45–7.53 (2H, m, $ArNO_2$), 8.13 (1H, d, J=10.4 Hz, NH), 8.21–8.28 (2H, m, $ArNO_2$); **3b**: R_f 0.06 (EtOAc:$CHCl_3$ 1:4); ^1H NMR ($CDCl_3$, 270 MHz) δ 3.60 (1H, d, J=12.7 Hz, H2), 4.04 (1H, d, J=12.7 Hz, H2), 4.57 (2H, s, PhOCH_2), 4.81 (1H, d, J=4.4 Hz, H6), 5.15 (1H, s, H4), 5.31 (2H, s, CO_2CH_2), 5.46 (1H, dd, J=4.4, 7.9 Hz, H7), 5.50 (2H, s, C3=CH_2), 6.90–7.10 (3H, m, Ph), 7.30–7.36 (2H, m, Ph), 7.39 (1H, d, J=8.1 Hz, NH), 7.52 (2H, m, $ArNO_2$), 8.26 (2H, m, $ArNO_2$). Both sets of data corresponded with those reported in the literature.[21,30]

*Thermal cyclization of sulfinyl pivaloate **14**.* Neat **14** (2 mmol) prepared above was heated at 75°C under 0.1 mmHg for 47 h. After being cooled to room temperature, the product was chromatographed (SiO_2, EtOAc:CH_2Cl_2 1:4) to provide cepham **3a** (311 mg, 31%) and cepham **3b** (101 mg, 10%).

*$Yb(OTf)_3$ catalyzed cyclization of sulfinyl pivaloate **14**.* A filtered solution of **14** (0.60 mmol) in dry MeOH free $MeNO_2$ (15 mL) was added to anhydrous $Yb(OTf)_3$ (37 mg, 0.06 mmol) and the mixture was stirred at room temperature for 23 h. The mixture was diluted with $CHCl_3$ (5 mL) and washed with H_2O (3×2 mL), brine (3 mL), dried ($MgSO_4$), filtered and evaporated to give a yellow foam (259 mg). Chromatography (SiO_2, EtOAc:$CHCl_3$ 1:4; EtOAc:$CHCl_3$ 4:6) gave cepham **3a** (99 mg, 33%) and cepham **3b** (31 mg, 10%).

*$Yb(OTf)_3$ catalyzed cyclization of sulfinyl chloride **2** in presence of NaOPv.* A filtered PhMe (21 mL) solution of **2** (0.60 mmol), prepared as described by Kukolja,[21,22] was stirred in the presence of fused $^tBuCO_2Na$ (85 mg of $^tBuCO_2Na.xH_2O$; x not specified, 0.6 mmol) and anhydrous $Yb(OTf)_3$ (37 mg, 0.06 mmol) for 40 h at room temperature. The product was diluted with $CHCl_3$ (5 mL) and washed with H_2O (3×2 mL), brine (3 mL), dried ($MgSO_4$), filtered and evaporated. Chromatography (SiO_2, EtOAc:$CHCl_3$ 1:4) gave cepham **3a** (146 mg, 49%) and cepham **3b** (11 mg, 4%).

*$Yb(OTf)_3$ catalyzed cyclization of sulfinyl chloride **2**.* Crude **2** (1.99 mmol), prepared as described by Kukolja,[21,22] was dissolved in dry MeOH free $MeNO_2$ (50 mL), filtered through a 0.45 μm PTFE syringe filter onto anhydrous $Yb(OTf)_3$ (124 mg, 0.06 mmol). The mixture was stirred at room temperature for 22 h, diluted with EtOAc (100 mL) and washed with H_2O (50 mL), a mixture of saturated aqueous $NaHCO_3$ and brine (1:1, 20 mL), brine (20 mL), dried ($MgSO_4$), filtered and evaporated to give a tan colored foam. The foam was dissolved in EtOAc (2 mL) and solids

allowed to precipitate. After removal of the filtrate, the precipitate was washed twice with EtOAc (1 mL) and dried under vacuum. The ^{1}H NMR spectrum of the crystalline solid was consistent with the product consisting of succinimide (13% of mixture) and 3-methylenecepham sulfoxide **3a** (87% of mixture: equivalent to 0.96 mmol, 48% yield).

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References

1. Marshman, R. W. *Aldrichim. Acta* **1995**, *28*, 77–84.
2. Kobayashi, S. *Synlett* **1994**, 689–710. Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W.-L. *Chem. Rev.* **2002**, *102*, 2227.
3. Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287–8288.
4. Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1997**, *62*, 232–233.
5. Kawada, A.; Mitamura, S.; Kobayashi, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1157–1158.
6. Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545–546.
7. Olah, G. A. *Friedel–Crafts Chemistry*. Wiley-Interscience: London, 1973.
8. Waller, F. J.; Barrett, A. G. M.; Braddock, D. C.; Ramprasad, D. *Chem. Commun.* **1997**, 613–614.
9. Barrett, A. G. M.; Braddock, D. C.; McKinnell, R. M.; Waller, F. J. *Synlett* **1999**, 1489–1490.
10. Barrett, A. G. M.; Braddock, D. C.; Henschke, J. P.; Walker, E. R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 873–878.
11. Barrett, A. G. M.; Braddock, D. C. *Chem. Commun.* **1997**, 351–352.
12. Waller, F. J.; Barrett, A. G.; M, .; Braddock, D. C.; McKinnell, R. M.; Ramprasad, D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 867–871.
13. Waller, F. J.; Ramprasad, D.; Barrett, A. G. M.; Braddock, D. C. In *Catalysis of Organic Reactions*; Herkes, F. E., Ed.; Marcel Dekker: New York, 1998; pp 289–305.
14. Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179–11180.
15. For examples see: Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*; 3rd ed.; Thieme: Stuttgart, 1999.
16. Morishita, T.; Furukawa, N.; Oae, S. *Tetrahedron* **1981**, *37*, 3115–3120.
17. Sheehan, J. C.; Henery-Logan, K. R. *J. Am. Chem. Soc.* **1962**, *84*, 2984–2990.
18. Animati, F.; Botta, M.; Angelis, F. D.; Dorigo, A.; Grgurina, I.; Nicoletti, R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2281–2286.
19. Chou, T. S.; Spitzer, W. A.; Dorman, D. E.; Kukolja, S.; Wright, I. G.; Jones, N. D.; Chaney, M. O. *J. Org. Chem.* **1978**, *43*, 3835–3837.
20. Wolfe, S.; Ducep, J.-B.; Tin, K.-C.; Lee, S.-L. *Can. J. Chem.* **1974**, *52*, 3996–3999.
21. Kukolja, S.; Lammert, S. R.; Gleissner, M. R. B.; Ellis, A. I. *J. Am. Chem. Soc.* **1976**, *98*, 5040–5041.
22. Kukolja, S. US Patent 4,081,440, 1978.
23. Barrow, K. D.; Spotswood, T. M. *Tetrahedron Lett.* **1965**, 3325–3335.
24. Kukolja, S.; Lammert, S. R. *Angew. Chem. Int. Ed.* **1973**, *12*, 67–68.
25. Baldwin, J. E.; Abraham, E. P.; Adlington, R. M.; Crimmin, M. J.; Filed, L. D.; Jayatilake, G. S.; White, R. L.; Usher, J. *J. Tetrahedron* **1984**, *40*, 1907–1918.
26. Spitzer, W. A.; Goodson, T.; Lammert, S. R.; Kukolja, S. *J. Org. Chem.* **1981**, *46*, 3568–3570.
27. Davis, M.; Wu, W.-Y.; Aust, *J. Chem.* **1987**, *40*, 1519–1526.
28. Kukolja, S. US Patent 4,052,387, 1977.
29. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1998.
30. Corfield, J. R.; Taylor, C. G. *Tetrahedron Lett.* **1978**, 2915–2918.