Aldehydes and ketones as dipolarophiles: application to the synthesis of oxapenams

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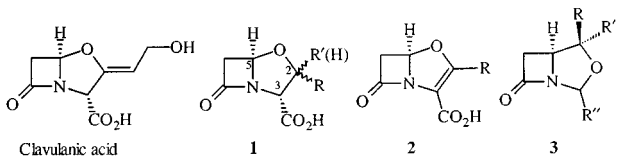
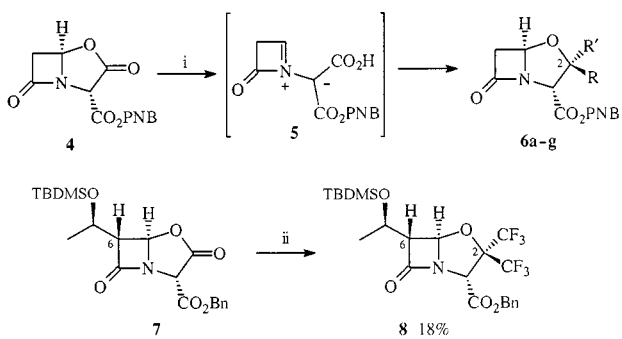
2-Substituted (6a–e) and 2, 2-disubstituted oxapenams (6f–g) are obtained in one step by thermolysis of the β-lactam-based oxazolidinone 4 in the presence of aldehydes and reactive ketones respectively; the *C(6)*-substituted oxazolidinone variant 7 reacts with hexafluoroacetone to give the enantiomerically pure oxapenam 8.

β-Lactams continue to represent a versatile and commercially significant class of antibiotics and the promise of an enhanced or novel biological profile has done much to stimulate the design and synthesis of new structural variants.[1] The oxygen-based clavams, of which the potent β-lactamase inhibitor clavulanic acid[2] is the best known example, also includes oxapenams **1**[3] and oxapenems **2**,[4] together with the isomeric isoclavams **3**.[5] These oxygen-containing bicyclic β-lactams,



which constitute an interesting and comparatively new class of β-lactams, incorporate significant strain as compared to their more stable sulfur-based analogues (penams). As a consequence, oxapenams are thermally and hydrolytically sensitive molecules, which places a significant demand on the range and efficiency of approaches that may be employed for the synthesis of these compounds.[6]

Here we describe a flexible but also very direct route for the synthesis of both 2-substituted and 2,2-disubstituted oxapenams represented by general structure **1**. The process that has been developed is summarised in Scheme 1 and involves a formal 1,3-dipolar cycloaddition reaction (to establish the bicyclic skeleton of the oxapenams) by exploiting aldehydes and reactive ketones as 1,3-dipolarophiles.[7] The successful application of this chemistry to oxapenams not only represents a novel entry to this class of molecule but also represents a significant

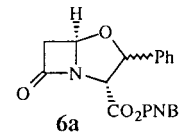
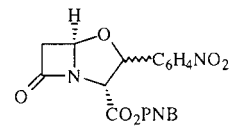
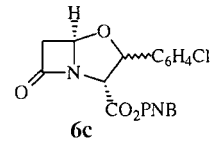
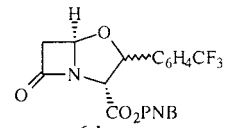
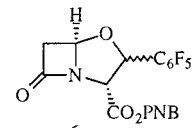
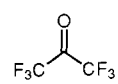
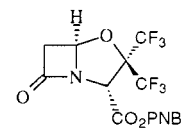
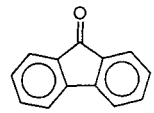
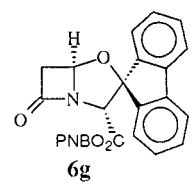


Scheme 1 *Reagents and conditions:* i, aldehyde/ketone (1.1–1.5 equiv.), MeCN, 81 °C, 24–48 h, then chromatography (for R and R′, see Table 1); ii, CF_3COCF_3, MeCN, 81 °C, 24 h.

extension to the recently reported azomethine ylide approach to bicyclic β-lactams.[8]

Thermolysis of the readily available β-lactam-based oxazolidinone **4** (PNB = $CH_2C_6H_4$-4-NO_2)[8] (which was carried out using deoxygenated MeCN, either at reflux or in a sealed tube at 81 °C) in the presence of either an aldehyde or a ketone (1.1–1.5 equiv.) provides racemic oxapenams **6a–g** in a single step albeit in moderate (19–56%) yield. The scope of this chemistry is illustrated by the examples shown in Table 1 and a

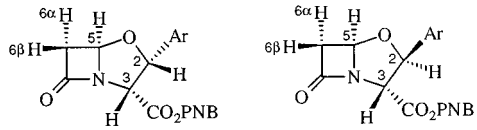
Table 1 Synthesis of oxapenams **6a–g**

Aldehyde/ketone	Oxapenam	Yield (%) (*exo* : *endo*)
PhCHO	 **6a**	19 (1 : 1)
4-$O_2NC_6H_4CHO$	 **6b**	21 (1 : 1)
4-ClC_6H_4CHO	 **6c**	26 (1 : 1)
4-$F_3CC_6H_4CHO$	 **6d**	21 (1 : 1)
C_6F_5CHO	 **6e**	40 (1 : 1.5)
	 **6f**	56
	 **6g**	25

range of 2-substituted oxapenams (derived from aldehydes) and 2,2-disubstituted oxapenams (derived from ketones) have been obtained. The same cycloaddition sequence has also been applied to the C(6)-substituted oxazolidinone variant **7**, which underwent reaction with hexafluoroacetone to provide the enantiomerically pure 2,2-bis(trifluoromethyl)oxapenam **8** {$[\alpha]_D^{24}$ +34.1 (*c* 0.09, CH_2Cl_2)} in 18% isolated yield.

The most important feature of the process shown in Scheme 1 is the very direct nature of this entry to oxapenams, which compensates for the modest yields observed. While aldehydes and reactive ketones appear to be reactive towards the azomethine ylide **5** (produced by fragmentation of **4**),[8c] a number of ketones (cyclohexanone, cyclopentanone, diethyl 2-oxomalonate, pyridine-4-carbaldehyde), either failed to trap or to give characterisable products. This may indicate the relative instability of the product oxapenams to either the thermal reaction conditions and/or chromatographic isolation, and such factors are likely contributors to the modest yields of oxapenams **6** that have been obtained.†

The cycloaddition pathway shown in Scheme 1 is, however, efficient in terms of the level of both regio- and stereo-control observed, but we were also concerned to establish this stereochemical outcome rigorously. Assignments in this area have often been based on the presumption that the thermodynamically more stable *trans* relationship between *C(3)* and *C(5)* predominates and by application of an empirical observation, the Bentley–Hunt rule.[6c] The reliability of this rule, and consequently its value as a diagnostic tool, has recently been questioned.[9] We, like others,[3c] have relied on NOE difference spectroscopy to assign the stereochemistry of oxapenams. With aldehydes, approximately equal amounts of the *exo* and *endo* adduct C(2) diastereomers were isolated and in the case of both **6d** and **6e**, the *exo* and *endo* isomers were separated and relative stereochemistry—C(2) *vs.* C(3) *vs.* C(5)—was assigned on the basis of NOE difference spectroscopy.‡ Only the oxapenam (clavam) regioisomer has been detected in the cases that we have examined and the thermodynamically more stable *trans* relationship between C(3) and C(5) (as defined by NOE and X-ray crystallography) is favoured; this latter stereochemical outcome is consistent with that observed previously in the synthesis of carbapenams, Δ^1-carbapenems and penams.[8]



exo-**6d**, Ar = $C_6H_5CF_3$ *endo*-**6d**, Ar = $C_6H_5CF_3$
exo-**6e**, Ar = C_6F_5 *endo*-**6e**, Ar = C_6F_5

The structure of the hexafluoroacetone adduct **6f** has been established by X-ray crystallographic analysis§ which confirmed both the regiochemistry of the cycloaddition reaction (clavam *vs*. isoclavam) and the relative stereochemistry between C(3) and C(5).

In summary, utilisation of aldehydes and reactive ketones as dipolarphiles for the azomethine ylide strategy provides a very direct entry to both 2-substituted and 2,2-disubstituted oxapenams. This not only represents a novel route to an unusual class of bicyclic β-lactams but also enhances the scope and value of the underlying cycloaddition based methodology.

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Notes and references

† Thermolysis of **4** in the presence of dibenzosuberone gave the corresponding cycloadduct in only 6% yield after 24 h, but on continued heating (to 48 h), complete decomposition of this product was observed. In a qualitative sense, we have observed a correlation between enhanced thermal and chromatographic stability of oxapenams and an increase in the electron withdrawing nature of the C(2) substituent(s).

‡ NOE difference analysis involved irradiation of all ring protons (H2, H3, H4, H6α and H6β). The proton irradiated is indicated in bold and the proton(s) enhanced are shown in brackets. *Exo*-**6d**: **H2** δ 5.61 (H3, H6β, *ortho* protons of $C_6H_4CF_3$); **H3** δ 5.08 (H2); **H5** δ 5.85 [H6α, H6β (weak)]; **H6α** (H5, H6β); **H6β** [H6α, H2, H5 (weak)]; *endo*-**6d**: **H2** δ 5.53 (H5, *ortho* protons of $C_6H_4CF_3$); **H3** δ 4.43 (*ortho* protons of $C_6H_4CF_3$); **H5** δ 5.53 [H2, H6α, H6β (weak)]; **H6α** (H5, H6β); **H6β** [H6α, H5 (weak)]. Similar observations (with the exception of the aromatic proton enhancements) were recorded for *exo*- and *endo*-**6e**. *Exo* and *endo* adducts for the other entries shown in Table 1 were readily correlated using ^{1}H NMR data. As illustrated for *exo*- and *endo*-**6d**, chemical shifts (300 MHz, CD_3CN) followed a clear pattern with signals for H2, H3 and H5 corresponding to the *exo* isomer consistently appearing at lower field than those associated with the isomeric *endo* adduct. The structure of cycloadduct **8** was also established by NOE spectroscopy. All new compounds have been characterised by spectroscopic methods and either microanalysis or high resolution mass measurement.

§ *Crystal data* for **6f**: $C_{15}H_{10}F_6N_2O_6$, M = 428.3, orthorhombic, space group *Pbca*, a = 11.658(1), b = 8.055(1), c = 36.764(5) Å, U = 3264.6(8) Å^3, Z = 8, μ = 0.177 mm^{-1}, 2344 unique data, θ < 23.3 °, R_1 = 0.032. CCDC 182/1118. The crystallographic data is available in CIF format, see: http://www.rsc.org/suppdata/cc/1999/249/

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