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A New Radical Route to C4-Unsubstituted β-Lactams

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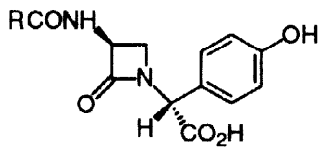
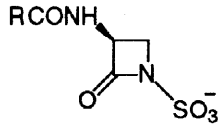
Abstract: C4-Unsubstituted β-lactams **3** are conveniently prepared from easily available 4-formyl-β-lactams **1**, in a sequential three step synthesis, using as the key step a radical reductive decarbonylation of 4-carboxy derivatives through their phenyl selenoesters **2**.

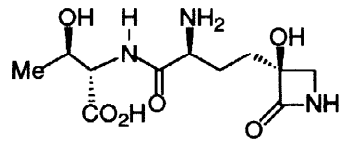
The powerful biological activity of nocardicins and monobactams against Gram negative organisms has highlighted the importance of developing efficient methods for the preparation of monocyclic 4-unsubstituted β-lactams.[1] Additionally, other relevant monocyclic β-lactams lacking substituents at position 4 of the 2-azetidinone ring such as tabtoxin,[2] and pachystermines[3] have been isolated from natural sources.



Nocardicins



Monobactams



Tabtoxin

Among the different methods for the synthesis of this particular type of monocyclic β-lactams,[4] the annelation of imines is probably the most used approach.[5] These routes rest on unstable, *in situ* generated, formaldehyde imines, or on the use of formaldehyde imine equivalents, namely substrates bearing a functionalized C=N double bond, to place an appropriate substituent at the C4 position of the 2-azetidinone ring which is further eliminated. While this work was in progress, Palomo *et. al.* have reported the first isolable and stable monomeric methanimine, and its Staüdinger reaction with ketenes.[6] However, regarding to the type of substituent at C3, the reported approaches to these monocyclic 2-azetidinones lack generality, and often they are obtained in racemic form. Work from our group has resulted in two different entries to C4-unsubstituted β-lactams based, respectively, on the desulfurization of 4,4-bis(methyltio)azetidin-2-ones with NiB_2,[7] and on the reduction with $NaBH_4$ of 4-(formyloxy) β-lactams.[8]

In this paper we report a general, simple, three-step synthesis of 4-unsubstituted-2-azetidinones **3** from 4-formyl-β-lactams **1**, which are easily available both in the racemic and optically pure forms.[9] This approach uses the reductive radical decarbonylation of 4-phenylselenocarbonyl-β-lactams **2**, following the method

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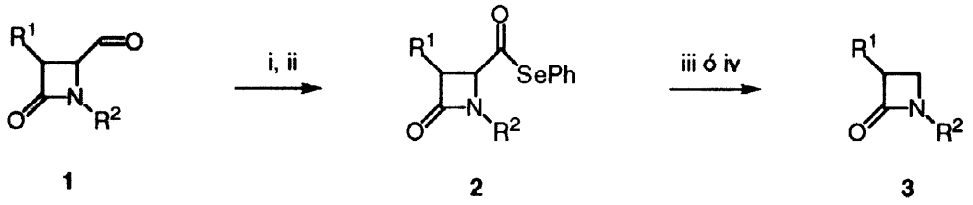
reported by Ireland for phenyl selenoesters adjacent to an oxygen atom (Scheme 1).[10] The reduction of α-nitrogenated selenoesters with tributyltin hydride (TBTH) is also known to give decarbonylated products.[11,12]



1 **2** **3**

i) CrO_3, H_2SO_4, acetone-water. ii) PhSeH, $PhOP(O)Cl_2$, Et_3N.
iii) TTMSS (2.2 equiv.), AIBN, C_6H_6, Δ. iv) Bu_3SnH (1.2 equiv.), AIBN, C_6H_6, Δ

Scheme 1

The starting substrates *cis*-4-formyl-β-lactams **1** were prepared using standard methodology previously reported by us.[8,9c-d] Sequential reaction of formyl-β-lactams **1** with Jones reagent, and benzeneselenol in the presence of dichlorophenyl phosphate/triethylamine, gave the phenylselenoesters **2**. Compounds **2** were enough stable to be isolated and purified by chromatography. However, purification was not required for the next synthetic step, and they were used as obtained. Radical reduction of selenoesters **2** either with TBTH or tris(trimethylsilyl)silane (TTMSS) in boiling benzene, gave the corresponding C4-unsubstituted β-lactams **3** in good yields.[13] The overall transformation, from compounds **1** to β-lactams **3**, occurs in fair to good yields (see Table). When optically pure starting material was used, the stereochemical integrity of the starting material remained unaltered.[14] This transformation tolerates alkyl-, aryl-, alkoxy, and amino substituents at the C3 of the 2-azetidinone ring as well as aryl, alkyl, and alkenyl groups on the lactam nitrogen atom.

Table. Synthesis of 4-Unsubstituted β-Lactams **3**[a]

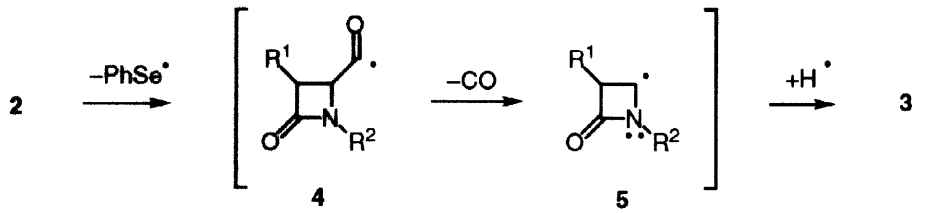
			Yield (%)[c]		
Comp.[b]	**R¹**	**R²**	**Method A**[d]	**Method B**[e]	**M.p.(°C)**[f]
3a	^{i}Pr	PMP[g]	85	80	70-72
3b	Ph	PMP	70	70	121-123
3c	PhO	PMP	80	60	92-94
3d	BnO	Benzyl	50		oil
3e	Ft	PMP	60	70	194-196
(+)-3f[h]	(*S*)-Ox[i]	PMP	45		198-199
(+)-3g[j]	BnO	PMP	58	50	94-96
(+)-3h[k]	PhO	Allyl		40	oil

[a] Starting substrates 1 were used in all cases as single cis-isomers. [b] With exception of **3e, 3g and 3h, all** compounds 3 were racemic mixtures. [c] Yield of pure, isolated product with correct analytical and spectral data. [d] Method A: TBTH was used as reductive reagent (see note 13); [e] Method B: TTMSS was used as reductive reagent (see note 13).[f] Crystallyzed from ethyl acetate/hexanes. [g] PMP = 4-methoxyphenyl. [h] Prepared from (+)-(3*S*,4*S*)-1-(*p*-anisyl)-4-formyl-3-[(*S*)-4-phenyl-2-oxo-oxazolidin-3-yl)]-2-azetidinone. [i]*S*-Ox = (*S*)-4-phenyl-2-oxo-1,3-oxazolidin-3-yl. [j] Prepared from (+)-(3*R*,4*R*)-1-(*p*-anisyl)-4-formyl-3-benzyloxy-2-azetidinone. [k] Prepared from (+)-(3*R*, 4*R*)-1-(*p*-anisyl)-4-formyl-3-phenoxy-2-azetidinone.

Although both methods gave, in general, analogous yields, TBTH required shorter reaction times (1-2 hours) than TTMSS (2-5 hours), and smaller amounts of reagent. Nevertheless, the choice of TMSS as reagent

to carry out the transformation of selenoderivatives **2** to final products **3**, is clear on the basis of easier purification of the crude reaction mixtures, and the fact that TBTH is less acceptable from ecological and toxicological perspectives.[15]

Formation of compounds **3** may be rationalized as shown in Scheme 2. As expected, the initially formed acyl radical **4** decarbonylates easily to the more stable azetidin-2-on-4-yl radical **5**.[16] The exclusive formation of compound **(+)-3h** from the corresponding 1-allyl substituted 4-formyl-β-lactam (+)-**1h**, proves that the rate for 5-exo-trig cyclization of acyl radical **4** is slower than decarbonylation to radical **5**.



Scheme 2

In conclusion, a scquential three-step synthesis of 4-unsubstituted β-lactams **3** starting from readily available 4-formyl-β-lactams **1** is reported. This new strategy is based on the radical reductive decarbonylation of 4-carboxy derivatives through their phenylselenoesters.

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13. A typical procedure follows: Jones reagent was added dropwise to a stirred solution of the 4-formyl-β-lactam **1** (1 mmol) in acetone (20 ml) until the reaction is complete (t.l.c.). Methanol (5 ml) was added and the reaction mixture was filtered through a short path of Celite. The filtrate was concentrated and taken in CH_2Cl_2 (10 ml) and water (5 ml). The aqueous layer was extracted (CH_2Cl_2, 2 x10 ml), dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The acid was used without further purification in the next step. To a solution of the above acid (1 mmol) in anhydrous THF (30 ml) under argon at 0 °C, Et_3N (3 mmol) and dichlorophenylphosphate (1.5 mmol) were added and the reaction mixture was stirred for 20 min. The resulting mixture was treated with PhSeH (1.5 mmol), stirred for 2h at 0 °C and then quenched with saturated solution of NaCl (5 ml). The selenoester derivative **2** was extracted (CH_2Cl_2, 3x 20 ml), dried ($MgSO_4$) and the solvent evaporated to yield a yellow oil which was either purified by column chromatography or used as such in the next step. Reductive decarbonylation was performed either with TBTH (*Method A*) or with TTMSS (*Method B*) (See Table). *Method A*: A mixture of the selenoester **2**, as crude product, (1 mmol), Bu_3SnH (1.2 mmol), and AIBN (0.2 mmol) was refluxed in dry benzene (40 mL) under argon. After completion of the reaction (t.l.c.), the solvent was evaporated to give an oil which was purified by flash chromatography and finally washed with pentane to yield the corresponding 4-unsubstituted β-lactams **3**. *Method B*: A mixture of the selenoester **2** (1 mmol), as pure product, $(Me_3Si)_3SiH$ (2.2 mmol), and AIBN (0.2 mmol) was refluxed in dry benzene (40 mL) under argon. After completion of the reaction (t.l.c.), the solvent was evaporated to give an oil which was purified by flash chromatography to yield product **3**. A four-fold excess of TTMSS was needed when selenoester was used as crude product.

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