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1,3-IMINOKETONES AS NEW SYNTHONS FOR THE STEREOCONTROLLED PREPARATION OF USEFUL CARBAPENEM INTERMEDIATES

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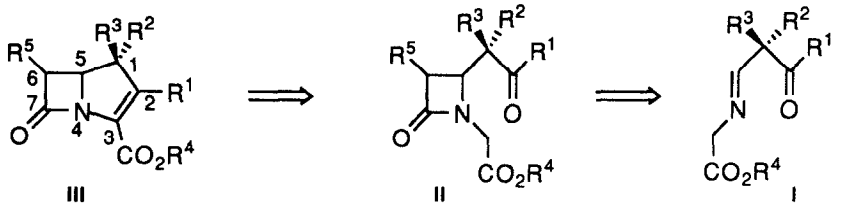
Abstract: An efficient, totally stereoselective two-step synthesis of *cis*- and *trans*-carbapenem intermediates based upon the reaction of *N*-methoxycarbonylmethyl 1,3-iminoketones **1** with benzyloxyacetyl chloride followed by a stereocontrolled intramolecular aldol-type condensation, has been developed.

The timely discovery of thienamycin and related carbapenems[1] triggered a still growing interest in the chemical synthesis of these antibiotics, since, in spite of their structural complexity, thienamycin and its *N*-formimidoyl analog iminipen are manufactured by total synthesis. In general, the synthesis of carbapenems (type **III**) has involved the development of efficient chemical synthesis of substituted monocyclic β-lactams, then formation of the bicyclic ring systems.[2,3] The most frequently used methods for the latter rely on an intramolecular Wittig-type reaction,[4] or its variants,[5] or a diazo insertion reaction.[6] Other methods such as aldol, Dieckmann, and related methodologies are less common.[7] Monocyclic *N*-alkoxycarbonylmethyl-β-lactams having a 2-oxoalkyl chain on the position 4 (type **II**) are classical synthons for the construction of the bicyclic skeleton through the aldol-type ring closure (Scheme 1). Routes to such useful intermediates have hitherto involved either multi-step transformation from appropriate 4-substituted β-lactams,[8,9] or multi-step, protecting-group manipulations starting from suitable 3-functionalized imines.[10]

In our ongoing program to develop readily available imine substrates as building blocks for β-lactam synthesis, and to apply new strategies for the synthesis of relevant types of monocyclic β-lactams,[11,12] we recently introduced 1,2-iminoketones[13] and 1,4-diaza-1,3-dienes (α-diimines)[14] as the starting materials for the direct access to functionalized 2-azetidinones. From the above background, we devised an entry to carbapenem intermediates of type **II** through the Staüdinger reaction of 1,3-iminoketones of type **I**, easily

accessible substrates which incorporate the required substituents on the imine group (Scheme 1). Compounds of type **I** have been used by us in related carbonyl addition reactions with lithium ester enolates.[15] Reported here is a new, efficient, and totally stereoselective two-step synthesis of both *cis*- and *trans*-carbapenem advanced intermediates based upon the reaction of *N*-methoxycarbonylmethyl 1,3-iminoketones **1** with benzyloxyketene followed by a stereocontrolled intramolecular aldol-type condensation on β-lactams **2**.

Scheme 1



Iminoketones **1**, obtained in nearly quantitative yield from the corresponding 3-oxoalkanals and methyl glycinate, reacted nicely with benzyloxyacetyl chloride in the presence of triethylamine to give exclusively the *cis*–β-lactams **2**. Cyclization of β-lactams **2** with lithium hexamethyldisilazide afforded either *cis*- or *trans*-2-hydroxy-1-carbapenams derivatives **3** and **4**, depending on the experimental reaction conditions (time and temperature) (Scheme 2). Thus, compounds *cis*-**3** were obtained by reaction at –78°C for 15 minutes while *trans*-**4** were the sole reaction products when longer reaction times (5 hours) were used. That *cis*-**3** are the sole products at short reaction times clearly shows that cyclization precedes isomerization in the formation of the *trans* isomers. However, basic epimerization of *cis*-**3** may not account for formation of *trans*-**4**. In fact, when

Table. Synthesis of monocyclic and bicyclic β-lactams **2**-**4**.

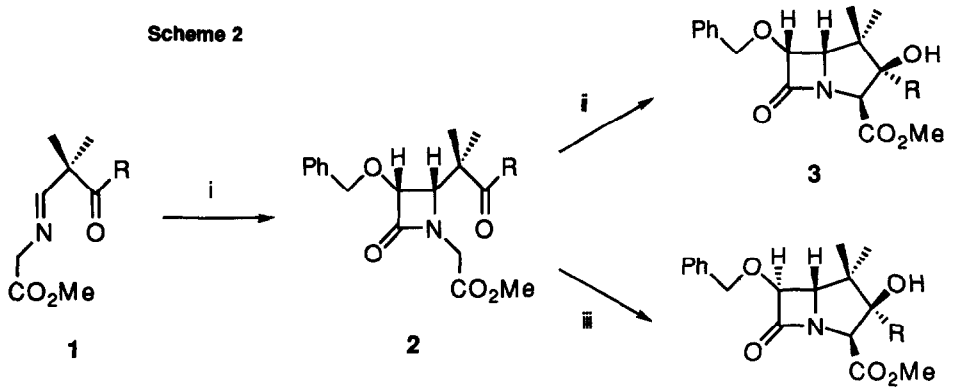
Comp.[a]	R	Yield (%)[b]	Mp (°C)[c]	^{1}H-nmr[d] H-5[e]	H-6[e]	$J_{5,6}$ (Hz)
2a	Me	70	oil	4.33	4.78	5.4
2b	Ph	86	oil	4.60	4.87	6.3
3a	Me	80	185-187	3.87	4.92	4.8
3b	Ph	70	182-184	4.13	4.95	4.8
4a	Me	70	oil	3.16	3.87	1.8
4b	Ph	70	oil	3.34	4.02	1.5

[a] All compounds were racemic mixtures with correct spectral and analytical data.[b] Of pure, isolated product.[c] Recrystallized from AcOEt-hexane. [d] Spectra recorded in $DCCl_3$ solution.[e] Proton numeration is based on the carbapenem nucleus.

cis-**3b** was subjected to reaction conditions analogous to those used to prepare *trans*-**4b**, complex reaction mixtures were obtained instead of the latter compound. Moreover, *trans*-**2a** is detected by monitoring (^{1}H NMR) the cyclization of *cis*-**2a** to *trans*-**4a**. Therefore, we propose that epimerization occurs on monocyclic *cis*-**2** prior to cyclization to *trans*-**4**, through an equilibrium between both, *cis*-**2** and *cis*-**3**.

All β-lactams **2-4** were obtained in good to excellent yields as stable, pure compounds (Table).[16] It is noteworthy that compounds **3** and **4** were always obtained as a single isomer . Stereochemistry at C5 and C6 follows immediately from the well established values for $J_{5,6}$ coupling, while the depicted (Scheme 2) relative stereochemistry at C2 and C3 for compounds **3** and **4** was established from NOE and NOESY experiments. Our stereochemical results may be accounted for in terms of chelated transition states **5** (*cis* or *trans* at C5-C6) (Scheme 3)[17] which would lead to **3** and **4**. Other transition states, such as **6**, would give rise to *anti* stereochemistry for OH and CO_2Me groups, (i. e. **7**), and are assumed to be less favorable.

Scheme 2

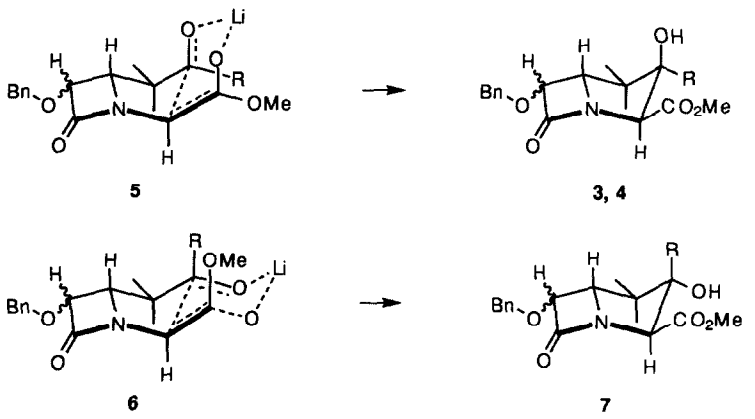


i: $PhCH_2OCH_2COCl$, Et_3N, toluene, r. t.;
ii: $LiN(TMS)_2$, THF, 5-15 min, –78°C;
iii: $LiN(TMS)_2$, THF, 5 h, –78°— r. t.

The procedure reported above is a very direct synthesis of 6-benzyloxy substituted 1,1-dimethyl-carbapenams which are the methyl analogs of the well known 1β-methyl carbapenem. Furthermore, it may be possible to manipulate the benzyloxy group at C6 to obtain unsubstituted or differently substituted carbapenems, by using well established standard methodology.[18] Finally, compounds related to **3a** have been converted into 1-carbapen-2-em derivatives[8,10] making the process reported here an efficient and selective entry to this family of antibiotics.

In conclusion, 1,3-iminoketones **1** are simple, useful synthons for the preparation of *cis*-β-lactams **2** which in turn can be used for the straightforward preparation of either *cis*- or *trans*-1-carbapenam derivatives through a stereocontrolled process. Work to determine the scope of the above synthetic process as well as the utility of compounds **1** in the preparation of other related bicyclic β-lactams is now in progress.

Scheme 3



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16. The following experimental procedures for preparation of compounds **2b** and **3b** are illustrative: **Compound 2b**. A solution of benzyloxyacetyl chloride (0.28 g, 1.5 mmol) in anhydrous benzene (5 ml) was added dropwise *via* syringe to a solution of the corresponding imine (0.25 g, 1 mmol) and Et_3N (0.30 g, 3 mmol) at room temperature under argon. The mixture was stirred for 24 h., then diluted with CH_2Cl_2 (15 mL) and washed with aqueous $NaHCO_3$ (saturated solution, 2 x 10 mL) and water (2 x 10 mL), and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the residue was purified by chromatography (florisil, first benzene to separate unreacted materials, then ether) to yield 0.35 g (86 %) of **2b** as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 3.70 (d, 1H, J = 17.7 Hz, NCH_2CO), 3.76 (s, 3H, OCH_3), 4.43 (d, 1H, J = 17.7 Hz, NCH_2CO), 4.49 (d, 1H, J= 5.8 Hz, H4), 4.64 (d, 1H, J = 13.6 Hz, CH_2Ph) 4.86 (d, 1H, J = 5.8 Hz, H3), 4.90 (d, 1H, J = 11.5 Hz, CH_2Ph), 7.31-7.48 (m, 8H, Ar), 7.58 (d, 2H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$): 208.1 (CO), 169.3 (COO), 168.4 (CON), 137.6, 136.9, 131.1, 128.4, 128.3, 128.0, 127.8, 127.7, 82.2 (C3), 73.4 (CH_2Ph), 64.4 (C4), 52.3 (CH_2CO), 48.9 (C-Me_2), 21.5 (CH_3).IR ($CHCl_3$): 1770 (CON), 1755 (COO), 1710 (CO) cm^{-1}. Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.84; H, 6.38; N, 3.54. Found: C, 70.02; H, 6.17; N, 3.49. **Compound 3b**. A solution of lithium bis(trimethylsilyl)amide in THF (10 mL) generated from hexamethyldisilazane (0.5 mL, 2.6 mmol) and BuLi (1.5 mL, 1.6 M in hexanes) cooled to -78 °C, was transferred *via* cannula under argon to a solution of β-lactam **2b** (0.7 g, 1.7 mmol) in anhydrous THF (15 mL) cooled to -78 °C. The resulting solution was stirred at -78 °C for 5 min and quenched with 2 mL of saturated NH_4Cl. The reaction mixture was allowed to warm to room temperature and was diluted with $CHCl_3$ (10 mL), and washed with water (2 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was recrystallized from an hexane/EtOAc mixture to yield 0.5g (70 %) of pure **3b** as colorless solid (mp. 185-187 °C).^1H NMR (300 MHz, $CDCl_3$), δ 0.76 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.13 (d, 1H, J = 5.1 Hz, H5), 4.60 (d, 1H, J = 12 Hz, CH_2), 4.82 (d, 1H, J = 12 Hz, CH_2), 4.95 (d, 1H, J = 5.1 Hz, H6), 5.14 (s, 1H, NCHCO), 7.24-7.44 (m, 10H, Ar). ^{13}C-NMR (75 MHz, $CDCl_3$), δ 178.3 (COO), 170.5 (CON), 137.7, 128.5, 128.2, 128.0, 127.6, 93.0 (COH), 80.3 (C_3), 73,7 (CH_2O), 66.0 (C4), 64.2 (CH), 52.8 (CMe_2), 50.1 (OCH_3), 19.0 (CH_3), 18.3 (CH_3). IR ($CHCl_3$), ν 1770 (CON), 1730 (COO) cm^{-1}. Anal Calcd for $C_{23}H_{25}NO_5$: C, 69.84; H, 6.38; N, 3.54 Found: C, 69.56; H, 6.28; N, 3.50.

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