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SYNTHESIS OF 3-AMINOALKYL SUBSTITUTED CARBAPENEMS VIA
A PHOSPHORANE INTERMEDIATE

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Abstract: Reaction of azetidinone phosphoranes **1** with aldehyde **2** gave the olefins **3**, which were converted into carbapenem esters **4** in 4 steps. Hydrogenation of **4** gave the title compounds.

In our search for carbapenems with better chemical and biological stability² we wanted to synthesize carbapenems substituted in the 3-position with aliphatic side chains, preferably provided with a basic functionality. The four general³ syntheses known for this class of compounds have their limitations: In the two Merck procedures⁴ the variable side chain is introduced as Grignard or cuprate reagent onto an azetidinone aldehyde or thiol ester, which limits the choice of side chain substituent. The other two methods from Sanraku Ocean chemists⁵ and from us^{2b} have the advantage that derivation occurs at a late stage in the synthesis on a bicyclic intermediate, but they only serve to introduce side chains with strongly electron-withdrawing groups on the α -carbon atom.

Since very few reactions can be performed on the bicyclic carbapenem or 3-oxo-carbapenam system without opening at least one of the two rings⁶ we preferred to introduce the variable side chain on an azetidinone intermediate. As it turns out, the azetidinone phosphorane **1a**⁷ is a very suitable intermediate: not only is it chemically very stable, but also, its low basicity allows Wittig reaction with aldehydes that can have a wide range of substituents including acidic ones such as amides and alcohols. Phosphorane **1a** (mp. 152-155°C) was easily prepared from the previously synthesized bromo-ketone **2**^{2c} (see Scheme and Reaction conditions) in 90% yield. Optically active **1b** (mp. 164-165°C) was synthesized in a more direct way by reacting ester **3b** with 2.5 eq of $\text{Ph}_3\text{P}=\text{CH}_2$ ⁸ in THF at -20°C. Reaction of **1a** with PhCHO in refluxing toluene gave the expected olefin **3a** (only *trans*, mp. 112-114°C) in 60% yield. Woodward's elaboration⁹ via phosphorane **5a** (48%) gave carbapenem **6a** (61%) as a yellow solid (mp. 155-160°C). Short (20 min.) hydrogenation of **6a** did not produce the expected carbapenem potassium salt, instead, we only found carbapenam **7** as a mixture of 2 β ,3 β (22%) and 2 α ,3 α (6%) isomers¹⁰ which was separated by RP-18 chromatography ($\text{H}_2\text{O}-\text{CH}_3\text{CN}$, 0-10%). In spite of this discouraging result, we proceeded by reacting **3a** with protected aminoaldehyde **8**¹¹. This reaction took place at much lower temperatures (60-80°C) than the one with benzaldehyde. Presumably, the reaction is catalyzed by intramolecular hydrogen bonding between the amide NH and the developing alkoxy anion in the transition state.

1

1. a. $R^1 = R^2 = H$, (+)
 b. $R^1 = R^2 = H$, (+)
 c. $R^1 = H$, $R^2 = CH_3$, (+)
 d. $R^1 = CH_3$, $R^2 = H$, (-)

(±) 2

3

3. b. $R^1 = R^2 = H$, (+)
 c. $R^1 = H$, $R^2 = CH_3$, (+)
 d. $R^1 = CH_3$, $R^2 = H$, (-)

4

5

6

- 4,5,6. a. $R^1 = R^2 = H$, $R^3 = Ph$, (+)
 b. $R^1 = R^2 = H$, $R^3 = CH_2CH_2NHCO_2PNB$, (+)
 c. $R^1 = H$, $R^2 = CH_3$, $R^3 = CH_2CH_2NHCO_2PNB$, (opt.act.)
 d. $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_2CH_2NHCO_2PNB$, (opt.act.)

(±) 7

8

9

9. a. $R^1 = R^2 = H$, (+)
 b. $R^1 = H$, $R^2 = CH_3$, (opt.act.)
 c. $R^1 = CH_3$, $R^2 = H$, (opt.act.)

(±) 10

11

11. a. $R^1 = H$, $R^2 = CH_3$, (opt.act.)
 b. $R^1 = CH_3$, $R^2 = H$, (opt.act.)

Reaction conditions:

- $\underline{2} \rightarrow \underline{1a}$: i. PPh_3 , CH_2Cl_2 ii. NaHCO_3 , H_2O
 $\underline{3} \rightarrow \underline{1}$: $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$, $n\text{-BuLi}$, THF -78°C -20°C
 $\underline{1} \rightarrow \underline{4}$: RCHO , benzene or toluene, reflux
 $\underline{4} \rightarrow \underline{5}$: i. $\text{PNBO}_2\text{CCH}(\text{OH})_2$, benzene, azeotropic reflux. ii. SOCl_2 , Et_3N , THF, -20°C .
 iii. Ph_3P , THF, RT
 $\underline{5} \rightarrow \underline{6}$: Toluene, reflux
 $\underline{6} \rightarrow \underline{7}, \underline{9}, \underline{11}$: H_2 , Pd/C (10%), EtOAc , phosphate buffer pH 7
 $\underline{1a} \rightarrow \underline{10}$: i. 2.5 eq LDA , 5 eq HMPA , THF, -78°C . ii. CH_3I -78°C 0°C

The resulting olefin $\underline{4b}$ (only trans, mp. $118\text{--}121^\circ\text{C}$, 93%) was converted to the phosphorane $\underline{5b}$ (43%) which was cyclized to carbapenem $\underline{6b}$ (mp $143\text{--}146^\circ\text{C}$, 55%). Fortunately, hydrogenation of $\underline{6b}$ gave 3-(4-aminobutyl)-carbapenem $\underline{9a}$ in 84% yield after RP-18 chromatography and lyophilization.

Merck chemists discovered that introduction of a 4 β -methyl group on 3-thio substituted carbapenems greatly improved their stability towards renal dehydropeptidase¹². Synthesis of $\underline{9c}$ therefore seemed a worthwhile goal, particularly since $\underline{9a}$ had insufficient DHP-stability. Direct methylation (2.5 eq. LDA , HMPA , CH_3I) of $\underline{1a}$ did not give (+) $\underline{1c,d}$; all we could isolate (63% yield) was the unexpected elimination product $\underline{10}$. Better results were obtained when a 2:1 mixture of $\underline{3c}$ and $\underline{3d}$ ¹³ was treated with 2.5 eq. of $\text{Ph}_3\text{P}=\text{CH}_2$ in THF at -20°C overnight. After work-up and medium pressure chromatography we obtained pure α -methyl-phosphorane $\underline{1c}$ ¹⁴ (mp $153\text{--}155^\circ\text{C}$, 27%), a mixture of $\underline{1c}$ and $\underline{1d}$ (9%), and pure $\underline{3d}$ (27%) uncontaminated by $\underline{3c}$. Being more interested in the β -methyl-phosphorane $\underline{1d}$ we tried to equilibrate $\underline{1c}$ to $\underline{1d}$ (LDA , -78°C ; HOAc , -78°C). As this was unsuccessful we reacted recovered $\underline{3d}$ once more with $\text{Ph}_3\text{P}=\text{CH}_2$. This gave phosphoranes ($\underline{1c}:\underline{1d} = 19:81$) in 47% yield. Eventually, $\underline{1d}$ was obtained pure after rechromatography and crystallization (CH_2Cl_2 - $i\text{-Pr}_2\text{O}$, mp. $78\text{--}82^\circ\text{C}$) in 7% overall yield. Further elaboration of $\underline{1c}$ and $\underline{1d}$ to $\underline{6c}$ and $\underline{6d}$ proceeded uneventfully; no epimerization occurred in any of these steps and deliberate attempts to epimerize $\underline{4c}, \underline{5c}$ and $\underline{6c}$ to their β -methyl counterparts all remained fruitless. Hydrogenation of $\underline{6c}$ produced a mixture of $\underline{9b}$ (15%) and $\underline{11a}$ (21%) which was separable on RP-18 (H_2O - CH_3CN , 0-10%) allowing us to evaluate the effect of the conjugated double bond on biological activity. Hydrogenation of $\underline{6d}$ likewise produced a mixture of $\underline{9c}$ (44%) and $\underline{11b}$ (16%) but we were unable to separate this. Prolonged hydrogenation produced pure $\underline{9c}$ in 42% yield. Full experimental details and biological activity of these compounds will be published elsewhere.

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7. Selected spectral data (NMR spectra in CDCl_3 or D_2O , UV's and rotations in CH_2Cl_2 or H_2O): **1a**: ^1H NMR: δ 4.95(1H,ddq,J=49.0,7.0,6.3Hz,HCF), 3.99(1H,ddd,J=9.5,4.1,2.2Hz,H-4), 3.72(1H,br d,J=26.5Hz,HCP), 3.00(1H,dddd,J=20.2,7.0,2.2,1.4Hz,H-3), 2.82 and 2.55(2H,ABX, J_{AB} =14.4Hz,J=9.5,4.1Hz, CH_2), 1.42(3H,dd,J=24.4,6.3Hz, CH_3). **1b**: UV: λ_{max} =265,272,294 nm, $[\alpha]_{\text{D}}^{21}$ =+58.7°. **1c**: ^1H NMR: δ 3.67 (1H,dd,J=10.5,2.0Hz,H-4), 1.24 (3H,d,J=6.8Hz, $\alpha\text{-CH}_3$), $[\alpha]_{\text{D}}^{21}$ =+58.4°. **1d**: ^1H NMR: δ 3.86(1H,dd,J=4.9,2.4Hz,H-4), 1.22 (3H,d,J=6.5Hz, $\beta\text{-CH}_3$), $[\alpha]_{\text{D}}^{21}$ =-10.9°. **4a**: ^1H NMR: δ 7.58(1H,d,J=16.0Hz,=CH), 6.75 (1H,d,J=16.0Hz,=CH). **4b**: ^1H NMR: δ 6.84(1H,dt,J=16.1,7.1Hz,=CH), 6.18(1H,d,J=16.1Hz,=CH). **4c**: ^1H NMR: δ 6.89(1H,dt,J=16.3,7.0Hz,=CH), 6.25(1H,d,J=16.3Hz,=CH). **4d**: ^1H NMR: δ 6.87(1H,dt,J=15.8,7.0Hz,=CH), 6.21(1H,d,J=15.8Hz,=CH). **6a**: IR(KBr): 1796,1701 cm^{-1} . **6b**: IR(KBr): 1789,1709 cm^{-1} . **6c**: IR(KBr): 1800,1710 cm^{-1} , $[\alpha]_{\text{D}}^{21}$ =-54.6°. **6d**: IR(CH_2Cl_2): 1776,1726 cm^{-1} , $[\alpha]_{\text{D}}^{21}$ =-30.8°. **7(2 α ,3 α)**: ^1H NMR: δ 4.36(1H,d,J=7.2Hz,C-2). **7(2 β ,3 β)**: ^1H NMR: δ 3.82(1H,d,J=8.0Hz,C-2). **9a**: UV: λ_{max} =267 nm, IR(KBr): 1759 cm^{-1} . **9b**: UV: λ_{max} =243,267 nm, IR(KBr): 1774 cm^{-1} . **9c**: UV: λ_{max} =266 nm, IR(KBr): 1751 cm^{-1} . **10**: ^1H NMR: δ 6.39(1H,ddd,J=17.0,10.3,10.0Hz,H-6), 6.16(1H,dd,J=15.3,10.0Hz,H-5), 5.99(1H,dd,J=15.3,7.5Hz,H-4), 5.11(1H,dd,J=17.0,1.5Hz,H-7Z), 4.98(1H,dd,J=10.3,1.5Hz,H-7E), 3.69(1H,br d,J=26.6,H-1), 3.14(1H,dq,J=7.5,6.8Hz,H-3), 1.30(3H,d,J=6.8Hz, CH_3). **11a**: ^1H NMR: δ 6.85(1H,d,J=16.3Hz,=CH), 5.85(1H,dt,J=16.3,7.1Hz,=CH), IR(KBr): 1779 cm^{-1} , UV: λ_{max} =295 nm. **11b**: ^1H NMR: δ 7.01(1H,d,J=16.4Hz,=CH), 5.97 (1H, dt,J=16.4,7.0Hz,=CH).
8. The presence of LiBr is essential: With phosphorane prepared from $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$ and NaNH_2 (Instant ylid, Fluka) no reaction occurred.
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12. D.H. Shih, F. Baker, L. Cama, and B.G. Christensen, Heterocycles, 1984, **21**, 29.
13. From **3b**, by treatment with 3 eq of LDA in THF at -78°C , followed by CH_3I . C.P. Mak, unpublished results. See also ref 12.
14. Stereochemical assignment from NOE experiments performed on **6c** and **6d**: Irradiation at the 4-methyl frequency caused enhancement of the H-5 absorption in **6c** and not in **6d**.