SYNTHESIS OF DIOXOLANYLCLAVAM FROM TARTARIC ACID

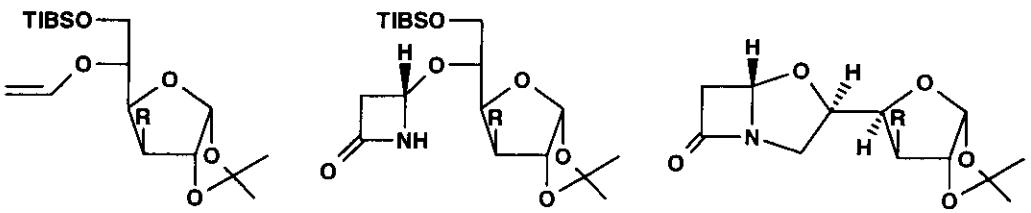
Oliver Neuß[b], Bartłomiej Furman[a], Zbigniew Kałuża[a], and Marek Chmielewski*[a]

[a]Institute of Organic Chemistry of the Polish Academy of Sciences, 01-224 Warsaw, Poland

[b]University of Bonn, Institute of Organic Chemistry and Biochemistry, D-53121 Bonn, Germany

Abstract-[2+2] Cycloaddition of chlorosulfonyl isocyanate to the 3-*O*-vinyl ether (**8**) derived from tartaric acid provides 4-alkoxy-azetidin-2-one (**9**) with 91.0% d.e.. Intramolecular *N*-alkylation afforded clavam (**11**) which corresponds to clavulanic acid missing the C-3 carboxylic function.

Recently we have reported on the formation of 4-alkoxy-β-lactams *via* asymmetric [2+2] cycloaddition of chlorosulfonyl isocyanate to 5-*O*-vinyl-D-glycofuranoses (**1**).[1] The stereoselectivity strongly depended on the substitution and on configuration at the C-3 carbon atom. A small substituent R at C-3 or allo configuration of the sugar promote excellent stereoselectivity to afford (S) configuration at the C-4' carbon atom of the azetidinone ring (**2**). Intramolecular alkylation of the nitrogen atom provided the corresponding clavam (**3**).[1]

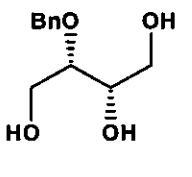


1 **2** **3**

TIBS = 2,4,6-triisopropylbenzenesulfonyl; R=OBn, $OCHPh_2$, OMe, OCH_2SMe, H.

Our results[1] obviously indicated that the furanoid ring was not necessary to get high asymmetric induction. It could be replaced by any other five membered ring, for example by a 1,3-dioxolane ring. This reasoning

lead to the conclusion that compound (**8**) possessing the 1,3-dioxolane ring instead of the furanoid fragment, with inverted configuration at the stereogenic centre bearing the vinyl ether group should give high asymmetric induction with opposite configuration (R) at the C-4' carbon atom of the azetidinone ring (**9**). Compound (**8**) was obtained by the standard reaction sequence from tartaric acid.



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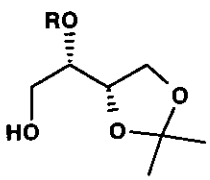
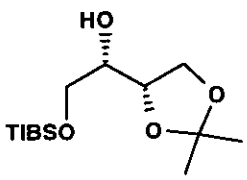


5: R=Bn

6: R=H



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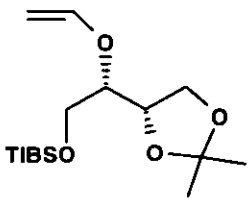

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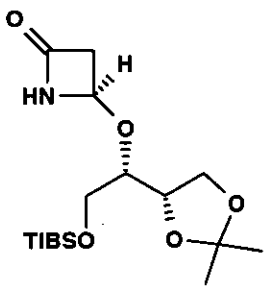
The known compound (**6**)[3,4] was obtained from **4**[2-5] using standard transformations involving formation of acetonide (**5**)[6] followed by debenzylation with sodium in liquid ammonia. Introduction of the sulfonyl substituent onto the primary hydroxyl group and the vinyl group [7] onto the secondary hydroxyl group gave compound (**8**). [2+2] Cycloaddition of chlorosulfonyl isocyanate to **8** was performed (according to the procedure described earlier) in toluene at -78 °C in the presence of sodium carbonate.[8] The chlorosulfonyl group was removed from the nitrogen atom by sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) reduction. The adducts (**9**) and (**10**) were obtained in 95.5 : 4.5 ratio. The configuration of **9** was assigned by intramolecular alkylation to afford the corresponding clavam (**11**). Alkylation was carried out in good yield using a two-phase system according to the known procedure.[1,9] The minute amount of the (5S) diastereomer (**12**), derived from the adduct (**10**), was isolated by chromatography during purification of **11**. NOE measurements showed spin interaction between H-3 and H-5 protons in **12**, whereas in the case of **11** such interactions were not observed. Compound (**11**), thus obtained, corresponds structurally to clavulanic acid (**13**) missing the C-3 carboxylic function.



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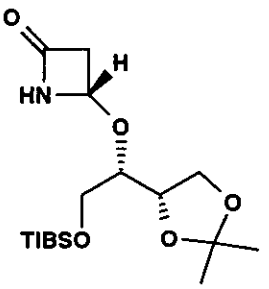

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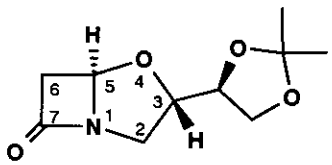
While quite a number of natural clavams have been isolated,[10] which have the (5R) configuration at the ring junction, only **13** and its simple *O*-acyl derivatives are known, so far, to possess strong β-lactamase

inhibition and weak antibacterial activity. Other clavams which possess the (S) configuration at C-5 exhibit activity against a number of species of fungi.[10]



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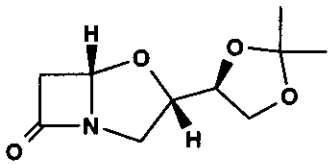

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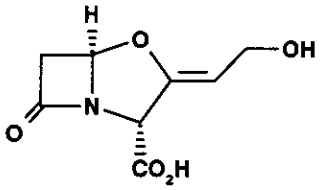

13

Compound (**11**) does not display antibacterial activity, whereas it shows anti β-lactamase activity in a composition with ampicilin; concentration of 8.5μg/ml of **11** decreases MIC of the antibiotic ampicilin resistant E. coli from 64μg/ml to 8μg/ml.

EXPERIMENTAL

Optical rotations were measured with a JASCO Dip-360 digital polarimeter. Ir spectra were obtained with a FT-IR-1600 Perkin-Elmer spectrophotometer. ^{1}H-Nmr spectra were recorded with a Bruker AM 500 spectrometer. Mass spectra were recorded with a AMD 604 mass spectrometer. Column chromatography was performed on Merck Kiesel gel (230-400 mesh). Compound (**4**) was obtained according to known procedures.[2-5]

(2S, 3S)-3-*O*-Benzyl-1,2-*O*-isopropylidene-L-threitol (5). Known compound (**5**) was obtained according to the general procedure described earlier (69 %).[3-5]

(2S, 3S)-1,2-*O*-Isopropylidene-L-threitol (6). Compound (**5**) (1.8g 7.14 mmol) in dry tetrahydrofuran (10 ml) was added to a stirred solution of sodium metal (1.2 g, 52 mmol) in liquid ammonia (100 ml). The mixture was stirred for 30 min at -78°C, then solid ammonium chloride was added to destroy the excess sodium. After removing the cooling bath, the solvent was evaporated and the residue was partitioned between water and THF. The aqueous layer was extracted three times with 30ml portions of t-butyl methyl ether. The combined organic extracts were dried over magnesiun sulfate, filtered and concentrated to

dryness, yielding **6**[3,4] (1.16 g, ~100 %) as a light-brown oil. $[\alpha]_D$ +4.3° (*c*=1.8, CH_3OH) (lit.,[4] $[\alpha]_D$ +3.9° (*c*=1.4, CH_3OH)).

(2S, 3S)-4-*O*-(2,4,6-Triisopropylbenzenesulfonyl)-1,2-*O*-isopropylidene-L-threitol (**7**). To a solution of compound (**6**) (1.9 g, 11.7 mmol) in dry pyridine (20 ml) TIBSCl (4.26 g, 14 mmol) was added at 0°C. After 60 h at 10°C the reaction mixture was diluted with water (100 ml). The brown solution was extracted three times with 40 ml portions of dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel using hexane-ethyl acetate 4:1 (v/v) as eluent, to give **7** (2.6 g , 52 %) as a colourless solid, mp 67-68 °C; ir (CH_2Cl_2) ν 3557 cm^{-1}; ^{1}H-nmr (500 MHz, $CDCl_3$) δ : 1.26 (d, *J* 6.9 Hz, 6H, TIBS), 1.27 (d, *J* 6.8 Hz, 12H, TIBS), 1.34 (d, *J* 0.4 Hz, 3H, Isopr.), 1.41 (d, *J* 0.4 Hz, 3H, Isopr.), 2.92 (sept, *J* 6.9 Hz, 1H, TIBS), 3.85 (dq, 1H, H-3), 3.88 (dd, *J* 8.4, 6.4 Hz, 1H, H-1a), 4.06 (m, 3H, H-1a, 4a, 4b), 4.13 (sept, *J* 6.7 Hz, 2H, TIBS), 4.21 (ddd, *J* 6.7, 6.4, 3.9 Hz, 1H, H-2), 7.20 (s, 2H, Aryl); $[\alpha]_D$ +0.55° (*c*=5.4, CH_2Cl_2); ms (EI, HR), m/z ; M^+ calcd for $C_{22}H_{36}O_6S$: 428.2233. Found : 428.2230. *Anal.* Calcd for $C_{22}H_{36}O_6S$: C, 61.65; H, 8.42; S, 7.48. Found : C, 61.60; H, 8.73; S, 7.83.

(2S, 3S)-4-*O*-(2,4,6-Triisopropylbenzenesulfonyl)-1,2-*O*-isopropylidene-3-*O*-vinyl-L-threitol (**8**). A solution of **7** (0.43 g, 1 mmol) and mercuric(II) acetate (0.008 g, 0.025 mmol) in butyl vinyl ether (15ml) was refluxed for 5 h. The solution was cooled, washed twice with saturated aqueous sodium carbonate, dried over magnesium sulfate, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel using hexane-ethyl acetate 12:1 (v/v) as eluent, to give **8** (0.38 g, 82 %) as a colourless oil. Ir (CH_2Cl_2) ν 1637cm^{-1}; ^{1}H-nmr (500 MHz, $CDCl_3$) δ : 1.26 (3d, *J* 6.7, 6.7, 6.9 Hz, 18H, TIBS), 1.32 (d, *J* 0.4 Hz, 3H, Isopr.), 1.36 (d, *J* 0.4 Hz, 3H, Isopr.), 2.91 (sept, *J* 6.9 Hz, 1H, TIBS), 3.84 (dd, *J* 8.7, 6.4 Hz, 1H, H-1a), 4.03 (dd, *J* 8.7, 6.7 Hz, 1H, H-1b), 4.05 (dd, *J* 6.5, 2.2 Hz, 1H, H-2'a), 4.12 (m, 3H H-3, 2×TIBS), 4.15(dd, *J* 10.7, 6.3 Hz, 1H, H-4a), 4.22 (dd, *J* 10.7, 4.4 Hz, 1H, H-4b), 4.29 (ddd, *J* 6.7, 6.5, 4.6 Hz, 1H, H-2), 4.33 (dd, *J* 14.1, 2.2 Hz, 1H, H-2'b), 6.30 (dd, *J* 14.1, 6.5 Hz, 1H, H-1'), 7.19 (s, 2H, Aryl); $[\alpha]_D$ +0.44° (*c*=5.5, CH_2Cl_2); ms (EI, HR) m/z , $(M - CH_3)^+$: calcd for $C_{23}H_{35}O_6S$: 439.2154. Found: 439.2161. *Anal.* Calcd for $C_{24}H_{38}O_6S$: C, 63.41; H, 8.42; S, 7.05. Found : C, 63.27; H, 8.57; S, 6.91.

(2S, 3S, 4'R)- and (2S, 3S, 4'S)-3-*O*-(Azetidin-2'-on-4'-yl)-3-*O*-(2,4,6-triisopropylbenzenesulfonyl)-1,2-*O*-isopropylidene-L-threitol (9 and 10). To a well stirred solution of sodium carbonate (0.032 g, 0.30 mmol) and chlorosulfonyl isocyanate (0.042 g, 0.30 mmol) in dry toluene (1ml) was added under

argon atmosphere at -70 °C a solution of **8** (0.1 g, 0.22 mmol) in dry toluene (1ml) within 5 min. The mixture was stirred at the same temperature for another 5 min and then was diluted with toluene (2.25 ml). Red-Al (375 µl of 1M solution in toluene, 0.375 mmol) was added slowly and the reaction mixture was stirred for 30 min. The cooling bath was removed and water (125 µl) was added at 0 °C. After an additional 15 min of intensive stirring the suspension was filtered and the solvent was evaporated. The residue was purified by column chromatography on silica gel using hexane-ethyl acetate 1:1 (v/v) as eluent, to give a mixture of **9** and **10** in proportion 95.5:4.5 (0.025 g, 25 %) as a colourless solid, mp 97-99°C; ir (CH_2Cl_2) ν 1775, 3417 cm^{-1}; ^{1}H-nmr (500 MHz, $CDCl_3$) δ : 1.26 (d, *J* 6.9 Hz, 12H, TIBS), 1.27 (d, *J* 6.8 Hz, 6H, TIBS), 1.33, 1.37 (2s, 6H, Isopr.) 2.77 (ddd, *J* 15.1, 1.4, 0.7 Hz, 1H, H-3'a), 2.92 (sept, *J* 6.9 Hz, 1H, TIBS), 3.08 (ddd, *J* 15.1, 4.0, 2.5 Hz, 1H, H-3'b), 3.72 (dd, *J* 8.6, 7.0 Hz, 1H, H-1a), 3.77 (dt, *J* 7.0, 4.8, 4.8 Hz, 1H, H-3), 4.05 - 4.12 (m, 4H, H-1b, 2, 4a, 4b), 4.13 (sept, *J* 6.8 Hz, 2H, TIBS), 5.15 (dd, *J* 4.0, 1.4 Hz, 1H, H-4'), 6.55 (s, 1H, NH), 7.20 (s, 2H, Aryl), signals due to stereoisomer **(10)** < 5 % distinguishable by the ^{1}H-nmr analysis: 3.13 (ddd, 1H, *J* 2.7, 4.0, 15.0 Hz, H-3'b), 5.24(dd, 1H, *J* 1.5, 4.0 Hz, H-4') ; ms (EI, HR) m/z, M^+ calcd. for $C_{25}H_{39}NO_7S$: 497.2447. Found : 497.2442. *Anal.* Calcd for $C_{25}H_{39}NO_7S$: C, 60.34; H, 7.90; N, 2.81; S, 6.44. Found : C, 60.49; H, 7.94; N, 2.93; S 6.40.

(3S, 5R, 1'S)- and (3S, 5S, 1'S)-3-(2', 2'-Dimethyl-1', 3'-dioxolanyl-4')clavam (11) and (12). To a solution of **9** and **10** (0.11 g, 0.23 mmol) in acetonitrile (5 ml) was added tetrabutylammonium bromide (0.08 g, 0.23 mmol) and potassium carbonate (0.34 g, 2.6 mmol). The mixture was heated under reflux for 2 h, cooled, diluted with toluene (5 ml) and filtered. The colourless solution was washed with water (5 ml), dried over magnesium sulfate, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel using hexane-t-butyl methyl ether 1:1 (v/v) as eluent, to give **11** (0.030 g, 61 %) and **12** (0.0015 g, 3 %) as a colourless oils. Ir (CH_2Cl_2) ν 1783 cm^{-1}; ^{1}H-nmr (500 MHz, $CDCl_3$) δ : 1.37 (s, 3H, Isopr.), 1.45 (s, 3H, Isopr.), 2.85 (dd, *J* 16.2, 0.6 Hz, 1H, H-6a), 2.93 (ddd, *J* 11.4, 6.3, 0.9 Hz, 1H, H-2a), 3.27 (ddd, *J* 16.2, 2.7, 1.0 Hz, 1H, H-6b), 3.85 (dd, *J* 8.2, 6.9 Hz, 1H, H-5'a), 3.95 (dd, *J* 11.4, 7.1 Hz, 1H, H-2b), 4.06 (dd, *J* 8.2, 6.7 Hz, 1H, H-5'b), 4.13 (ddd, *J* 6.9, 6.7, 4.0 Hz, 1H, H-4'), 4.37 (ddd, *J* 7.1, 6.3, 4.0 Hz, 1H, H-3), 5.38 (bd, *J* 2.7 Hz, 1H, H-5); $[\alpha]_D$ +3.7° (*c*=4.2, CH_2Cl_2); ms (EI, HR) m/z , $(M-CH_3)^+$ calcd. for $C_9H_{12}NO_4$: 198.0766. Found : 198.078. *Anal.* Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found : C, 56.48; H, 7.05; N, 6.45. **Compound (12)** ^{1}H-Nmr (500 MHz, $CDCl_3$) δ : 1.36 (s, 3H, Isopr.), 1.44 (s, 3H, Isopr.), 2.91 (d, *J* 16.0 Hz, 1H, H-6a), 3.12 (ddd, *J* 11.0, 7.3, 0.8 Hz, 1H, H-2a), 3.25 (ddd, *J* 16.0, 2.6, 0.8 Hz, 1H, H-6b), 3.61 (dd, *J* 11.0, 6.3 Hz, 1H, H-2b), 3.74 (dd, *J* 8.4, 6.5 Hz, 1H, H-5'a), 4.05 (dd, *J* 8.4, 6.7 Hz, 1H, H-5'b), 4.17 (ddd, *J* 6.7, 6.5, 5.4 Hz, 1H, H-4'), 4.38 (bq, *J* 6.3, 6.4, 7.3 Hz, 1H, H-3), 5.24 (d, *J* 2.5 Hz, 1H, H-5).

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