Supporting Material

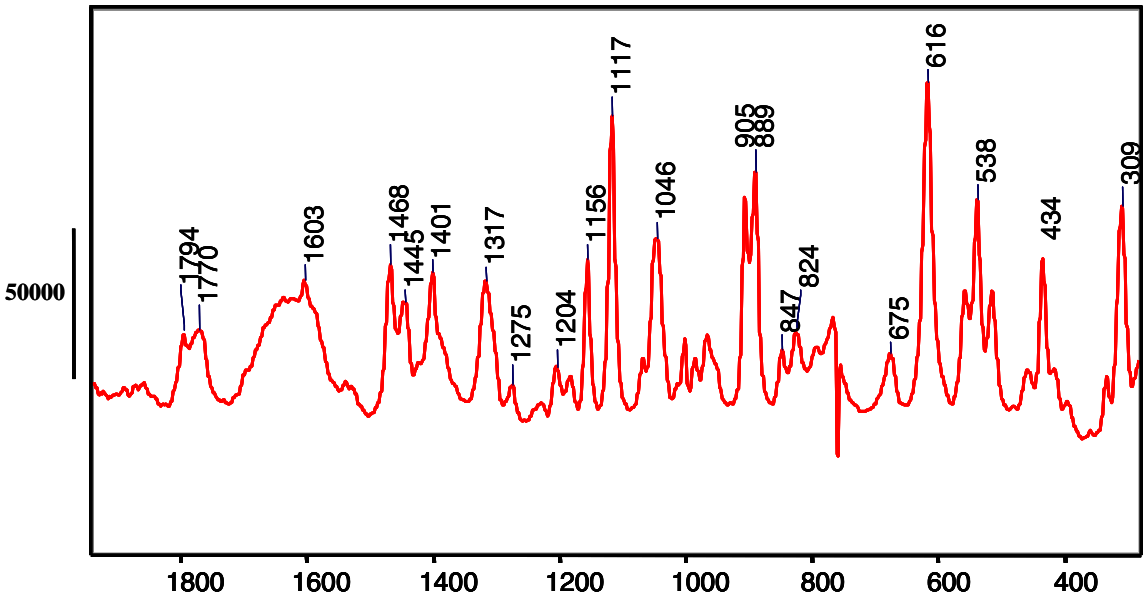


Figure 1: Raman spectrum of 6, 6 dideuterated sulbactam 20 mM in HEPES buffer 0.1M, pH 7

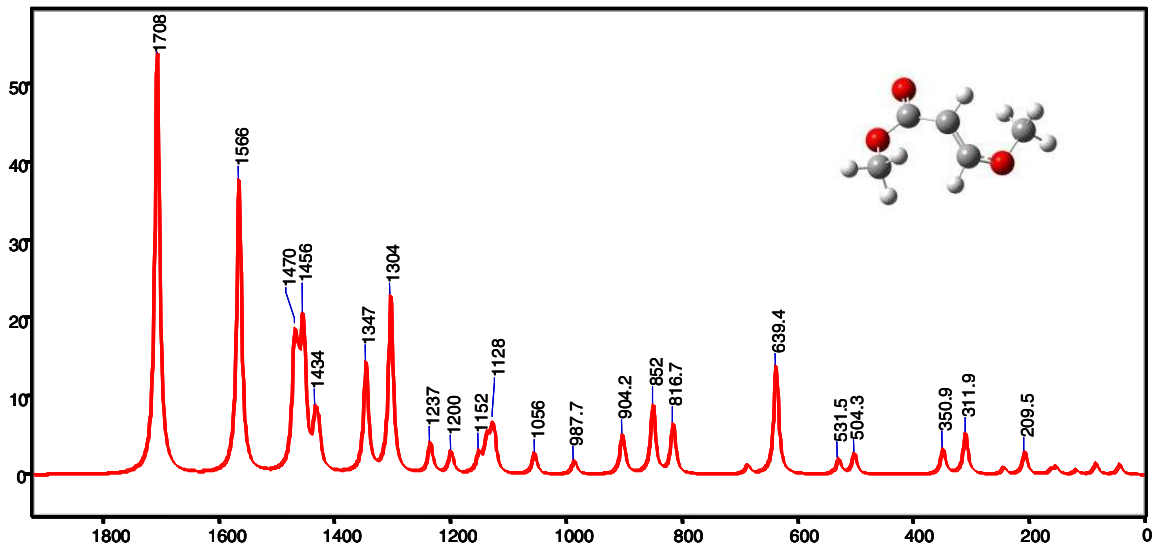
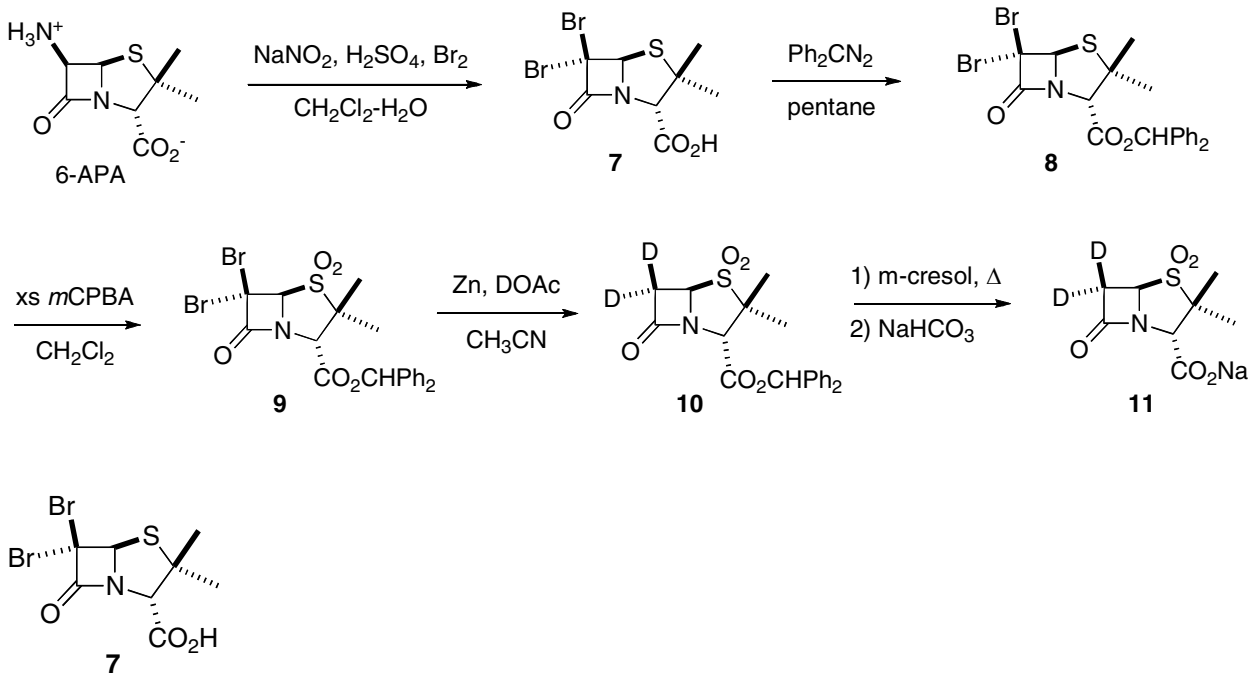


Figure 2: Calculated Raman spectrum of methyl 3-methoxyacrylate (species 5 in Scheme I), obtained by using the Gaussian 03 software, where the most intense features are detailed in parenthesis (1708 cm^{-1} C=O and C-H stretch, 1566 cm^{-1} C=C stretch and delocalized motion over the entire chain, 1470 cm^{-1} C-H bending and stretching over the entire chain, 1304 cm^{-1} C=C and C=O stretch, C-H bending)

Calculated Raman ν/cm^{-1} for $CH_3OCHCHCOOCH_3$/ $CH_3OCHCDCOOCH_3$-intensities are shown in parenthesis	**Assignment**
1707 (54)/1705 (53)	C=O stretch, CH wagging
1566 (37)/1551(45)	C=C, COO^- stretching, delocalized stretching over the entire chain
1470(14)/1470(13)	CH wagging from the methyl groups
1347 (14) /1344(19)	CH_3, CH wagging from C_3, delocalized stretching over the entire chain
1304 (22)	CH wagging from the C_2

Synthesis of 6,6-Dideuteropencillanic Acid Sulfone



6,6-Dibromopenicillanic acid (7). Prepared according to the procedure of Volkmann.[1] To a 3 L three-necked flask equipped with an overhead stirrer and thermometer was added CH_2Cl_2 (1.5 L) and the contents cooled to approx 5 °C. To the solvent was then added Br_2 (359.7 g, 115.5 mL, 2.25 mol), H_2SO_4 (2.5 N, 600 mL, 1.5 mol), and $NaNO_2$ (103.5 g, 1.5 mol). Some foaming was observed after the addition of the $NaNO_2$. 6-APA (162 g, 0.75 mol) was then added portion wise over a period of 30 min while maintaining the reaction temperature between 4 to 10 °C. The resultant dark red solution was stirred at 5 °C for 30 min. A solution of aq $NaHSO_3$ (1M, 1.23 L) was added dropwise at 5 to 15 °C over a period of 20 min until the color became light yellow. The organic layer was

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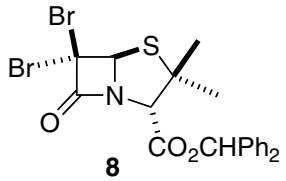
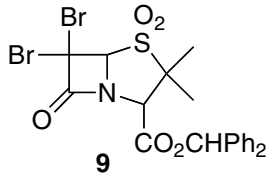
([1]) Volkmann, R. A.; Carroll, R. D.; Drolet, R. B.; Elliott, M. L.; Moore, B. S. (1982) Efficient Preparation of 6,6-Dihalopenicillanic Acids. Synthesis of Penicillanic Acid *S, S*-Dioxide (Sulbactam) *J. Org. Chem., 47*, 3344-3345.

separated and the aqueous layer extracted with additional CH_2Cl_2 (2 x 400 mL). The combined organic extracts were washed with brine (2 x 600 mL), dried over Na_2SO_4, and concentrated to give 229 g of crude product (crude yield = 85%). This material was utilized in the following reactions without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.59 (s, 3H), 4.62 (s, 1H), 5.82 (s, 1H), 6.93 (s. 1H), 7.33 - 7.36 (m, 10H).



8

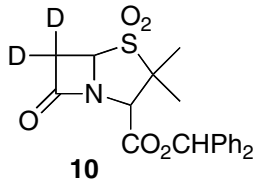
Benzhydryl 6,6-dibromopenicillinate (8). To a solution of 6,6-dibromopenicillanic acid, (420 g, 1.17 mol) in acetone (2 L) at 0 °C was added a solution of diphenyldiazomethane (250 g, 1.23 mol) in acetone (500 mL), and the resultant mixture was mechanically stirred for 20 h at rt. The solvent was then removed in vacuo and the resultant residue was purified by flash chromatography on silica gel (15% CH_2Cl_2/hexane) to produce pure benzhydryl ester (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (10H, m, Ar), 6.95 (1H, s, $CHPh_2$), 5.84 (1H, s, C5 CH), 4.63 (1H, s, C3 CH), 1.62 (1H, s, Me), 1.28 (1H, s, Me).



9

Benzhydryl 6,6-dibromopenicillinate sulfone (9). To a solution of sulfide (10.0 g, 19.04 mmol) in dichloromethane (100 mL) was added *m*CPBA (13.09 g, 76.16 mmol), then the reaction mixture was stirred at room temperature for 12 h. Sodium metabisulfite (10.0 g in 100 mL water) solution was added to the above mixture, layers were separated, organic layer was washed with aq $NaHCO_3$, water and brine (150 mL each). Then it was dried over Na_2SO_4, concentrated and purified by column chromatography using DCM as eluant to give 7.95 g of product (75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.58 (s, 3H), 4.60 (s, 1H), 4.99 (s, 1H), 6.96 (s. 1H), 7.31-7.39 (m, 10H).

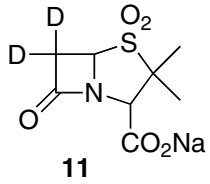


10

Benzhydryl 6,6-dideuteropenicillinate sulfone (10). To a stirred solution of dibromide **9** (1.0 g, 1.79 mmol) in acetonitrile (10 mL) at 0 °C was added AcOD (1.0 mL) and Zn powder (0.468g, 7.16 mmol) was added, the mixture was stirred at 0 °C for 1.5 h. Excess Zn was removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in DCM, washed successively with brine and dilute aq $NaHCO_3$, dried and concentrated. The residue was chromatographed on silica gel with 5% EtOAc/DCM as eluant to produce 0.429 g (60% yield) of dideuterated penicillin sulfone.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.55 (s, 3H), 4.49 (s, 1H), 4.54 (s, 1H), 6.96 (s. 1H), 7.28-7.35 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.24, 19.52, 37.57 (quintet, J = 20.8 Hz), 60.68, 62.59, 62.85, 78.8, 126.56, 127.5, 128.12, 128.47, 128.51, 128.59, 138.45, 138.68, 165.92, 170.71.

IR (KBr, cm^{-1}): 1118.76, 1185.06, 1322.75, 1455.28, 1495.18, 1755.42, 1802.1, 3583.63.



11

Sodium salt of 6,6-dideuteropenicillanic acid sulfone (11). To a solution of ester (350 mg, 0.872 mmol) in *m*-cresol (3.5 mL) was heated at 50 °C for 3 h under an argon atmosphere. The mixture was then cooled to rt, diluted with ether (10 mL) and treated with aq $NaHCO_3$ (80.0 mg was dissolved in 5 mL of deionized water, 0.959 mmol). The separated aqueous layer was then purified on a column of CHP2OP (Mitsubishi Chemical Corporation) using deionized water as eluent and lyophilized to give 80 mg (36% yield) of pure sodium salt.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 3H), 1.59 (s, 3H), 4.2 (s, 1H), 4.99 (s, 1H).

^{13}C NMR (100 MHz, D_2O): δ 20.65, 22.33, 39.43, 39.68 (quintet, J = 24.9 Hz), 63.93, 66.59, 68.18, 175.75, 177.84.