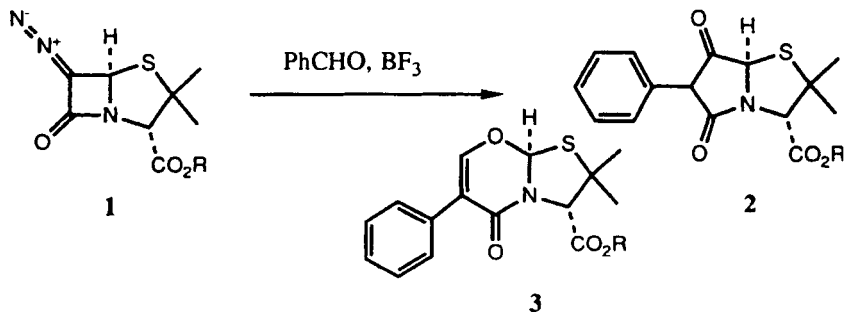# SYNTHESIS AND REARRANGEMENT OF DISPIRO-EPOXY-β-LACTAMS

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Abstract: α-Methylene-β-lactams are prepared by a Peterson olefination reaction. These substrates can be epoxidized with MCPBA to give the title dispiro-epoxy-β-lactams. Under the influence of boron trifluoride, these substrates rearrange to spiro-3-ketolactams.

As a class of compounds spiro-epoxy-β-lactams have not been well studied. Sheehan reported the preparation of spiro-epoxy-β-lactams by the reaction of 6-diazopenicillanate esters 1 with aldehydes in the presence of boron trifluoride.[1] From this research a number of additional products resulting from the rearrangement of the intermediate spiro-epoxy-β-lactam were reported. A report of John and Edwards later conflicted with the results of Sheehan.[2] Their report claimed that the product identified as 2 by Sheehan actually was the thiazolooxazinone 3. Their claims, refuting that of Sheehan's, were supported by an X-ray crystallographic analysis.

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Herein, we report a new synthesis of spiro-epoxy-β-lactams, and our results on their rearrangement under the influence of boron trifluoride. Starting with 1-(2,6-diethylphenyl)-3-trimethylsilyl-2-azetidinone (4) we proceeded with a Peterson reaction on cyclohexanone to give the α-methylene-β-lactam 5 in a 59% isolated yield. This was smoothly epoxidized with MCPBA in refluxing dichloroethane to give an 83% yield of the dispiro-epoxy-β-lactam 6.[3] Upon treatment of 6 in methylene chloride at 0°C with a catalytic amount of boron trifluoride etherate, we obtained a 67% yield of the spiro-3-ketolactam 7. This product results from a 1,2-carbonyl migration in a similar fashion to what Sheehan reported as giving 2. An analogous reaction has been reported in the literature in which dispiro-epoxy-ketones rearrange to give spiro-1,3-diketones.[4]
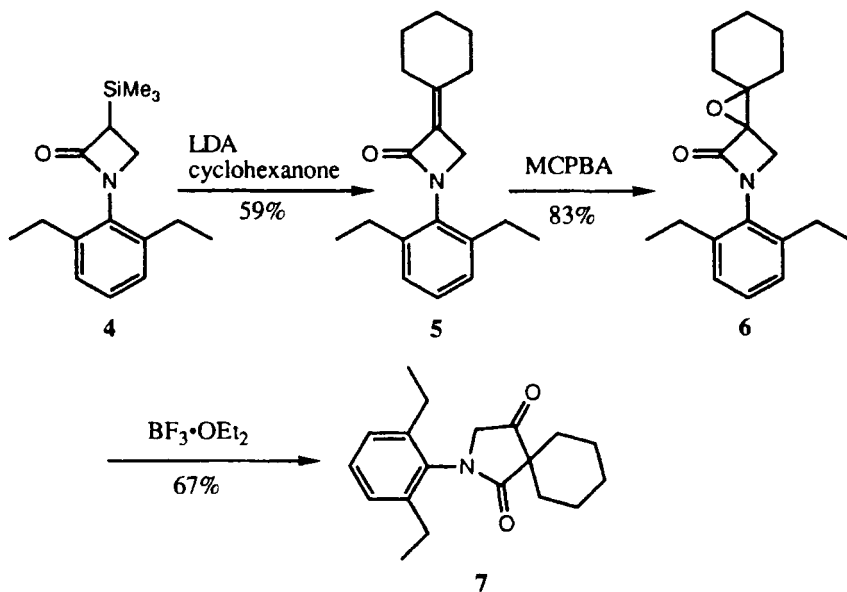
We have found that this reaction is only general for dispiro-epoxy-β-lactams like 6. The homologous dispiro-epoxy-γ-lactam 8 gave the hydroxy-olefin 9 upon treatment with boron trifluoride etherate. For each of these cases the fate of the intermediate carbonium ion is different. In the β-lactam case, a 1,2-carbonyl migration occurs. For the γ-lactam, elimination of a proton is favored. Apparently, the ring strain of the β-lactam is the driving force behind the 1,2-carbonyl migration. No α-ketolactams, from 1,2-alkyl migration, were detected in either case.
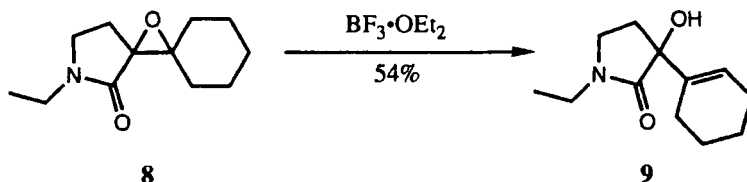
We feel the epoxidation of α-methylene-β-lactams to give spiro-epoxy-β-lactams is an improvement over the previously reported methods involving diazo-β-lactams. Epoxidation of α-methylene-β-lactams is a higher yielding and more general reaction than the reaction of α-diazo-β-lactams with aldehydes. The preparation of the α-methylene-β-lactams by a Peterson olefination of α-silyl-β-lactams, is a reaction that has established its utility in the literature.[5]

It is not surprising the spiro-epoxy-penicillanate esters reported by Sheehan, John, and Edwards undergo different reactions, under the influence of boron trifluoride, than the spiro-epoxy-β-lactams we have disclosed. Other mechanistic pathways, if presented, can be favored over the 1,2-carbonyl migration. The report by John and Edwards, and our results from the dispiro-epoxy-γ-lactam **8** are evidence to other pathways being favored.

Experimental Section

NMR spectra were recorded on an IBM AF-300 spectrometer. Chemical shifts are reported in units of ppm relative to the standard tetramethylsilane. Elemental analyses were performed by Atlantic Microlab, Inc. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Flash chromatography was performed on 230-400 mesh silica gel. Solvents and reagents were used as purchased.

1-(2,6-Diethylphenyl)-3-cyclohexylidene-2-azetidinone (5)
An LDA solution was generated by the addition of 21.2 mL (55 mmol) of a 2.6M n-butyllithium solution to a solution of 7.7 mL (55 mmol) of diisopropylamine in 150 mL of anhydrous tetrahydrofuran at -78°C under nitrogen. A solution of 1-(2,6-diethylphenyl)-3-trimethylsilyl-2-azetidinone[6](4) (13.77 g, 50 mmol) in 50 mL of anhydrous tetrahydrofuran was added to the LDA solution over a five minute period. After stirring at -78°C for 15 minutes, 6.2 mL (60 mmol) of cyclohexanone was added over five minutes. The dry ice bath was removed allowing the reaction to warm to room temperature followed by stirring for one hour. Quenched the reaction with water, diluted with 100 mL of ethyl acetate, and washed the mixture with water followed by brine. Dried organic phase over anhydrous magnesium sulfate. GC analysis indicates the mixture to be 73% of **5** and 25% of starting material. Purified by flash chromatography on silica gel (eluted with ethyl acetate : hexanes = 1:10) to give a solid that was *recrystallized from*

hexanes yielding 8.32 g (59% yield) of 5 as fine white flakes (MP 102 - 103 °C). ^{1}H NMR (CDCl₃): δ 1.22 (t, J = 7.57 Hz, 6H), 1.66 (m, 6H), 2.12 (br t, J = 5.33 Hz, 2H), 2.61 (q, J = 7.57 Hz, 4H), 2.68 (br t, J = 5.22 Hz, 2H), 3.99 (s, 2H), 7.11 (d, J = 7.73 Hz, 2H), 7.22 (dd, J = 8.35, 6.78 Hz, 1H); ^{13}C NMR (CDCl₃): δ 14.69, 24.97, 26.14, 27.59, 27.66, 30.25, 31.69, 50.15, 126.30, 127.51, 128.47, 133.40, 142.52, 143.66, 163.75; elemental analysis: calcd. for $C_{19}H_{25}NO$ - C, 80.52%; H, 8.89%; N, 4.94%; found - C, 80.50%; H, 8.89%; N, 4.92%.

2-(2,6-Diethylphenyl)-11-oxa-2-azadispiro[3.0.5.1]undecan-3-one (6)   A mixture of 7.00 g (24.7 mmol) of 1-(2,6-diethylphenyl)-3-cyclohexylidene-2-azetidinone, 10.6 g (49.4 mmol) of 80% m-chloroperoxybenzoic acid, 5.2 g (61.7 mmol) of sodium bicarbonate, and 10 mg of 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide in 100 mL of 1,2-dichloroethane was refluxed together under nitrogen for two hours. Quenched with 80 mL of a 20% sodium sulfite solution and stirred for 15 minutes. Separated the layers, and extracted the aqueous phase with methylene chloride. The combined organic phases were washed with a saturated sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Concentration gave an oil that was purified by flash chromatography on silica gel (eluted with ethyl acetate : hexanes = 1:10). Obtained 6.14 g (83% yield) of 6 as a yellow oil. ^{1}H NMR (CDCl₃): δ 1.23 (t, J = 7.59 Hz, 6H), 1.4 - 2.1 (m, 10H), 2.63 (br q, J = 7.33, 4H), 3.80 (d, J = 6.3 Hz, 1H), 3.91 (d, J = 6.3 Hz, 1H), 7.12 (d, J = 7.63 Hz, 2H), 7.25 (dd, J = 9.15, 6.04 Hz, 1H); ^{13}C NMR (CDCl₃): δ 14.77, 25.00, 25.21, 25.30, 30.24, 32.97, 51.06, 66.54, 73.37, 126.68, 128.97, 132.44, 142.25, 167.31; elemental analysis: calcd. for $C_{19}H_{25}NO_2$ - C, 76.22%; H, 8.42%; N, 4.68%; found - C, 75.78%; H, 8.46%; N, 4.59%.

2-(2,6-Diethylphenyl)-2-azaspiro[4.5]decan-1,4-dione (7)   A solution of 3.97 g (13.3 mmol) of 2-(2,6-Diethylphenyl)-11-oxa-2-azadispiro[3.0.5.1]undecan-3-one in 65 mL of methylene chloride was cooled in an ice bath at 0 °C. Boron trifluoride etherate (0.16 mL, 1.33 mmol) was added, the ice bath was removed, and the reaction was stirred at room temperature for one hour. Diluted the reaction with 50 mL of methylene chloride and washed with a saturated sodium bicarbonate solution. Dried the organic phase over anhydrous magnesium sulfate. The crude product was purified by flash chromatography on silica gel (eluted with ethyl acetate : hexanes = 1: 5), and recrystallized from hexanes to give 2.67 g (67% yield) of 7 as fine white needles (MP 107 -108 °C). ^{1}H NMR (CDCl₃): δ 1.21 (t, J = 7.56 Hz, 6H), 1.4 - 2.0 (m, 10H), 2.49 (m, 4H), 4.00 (s, 2H), 7.17 (d, J = 7.77 Hz, 2H), 7.30 (dd, J = 8.30, 6.91 Hz, 1H); ^{13}C NMR (CDCl₃): δ 14.43, 20.51, 24.17, 24.87, 29.67, 49.82, 56.67, 126.77, 129.03, 133.27, 141.63, 174.91, 210.47; elemental analysis: calcd. for

$C_{19}H_{25}NO_2$ - C, 76.22%; H, 8.42%; N, 4.68%; found - C, 76.08%; H, 8.47%; N, 4.61%.

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