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Synthetic Routes for the Generation of 7,7-Dialkyl Azepin-2-ones

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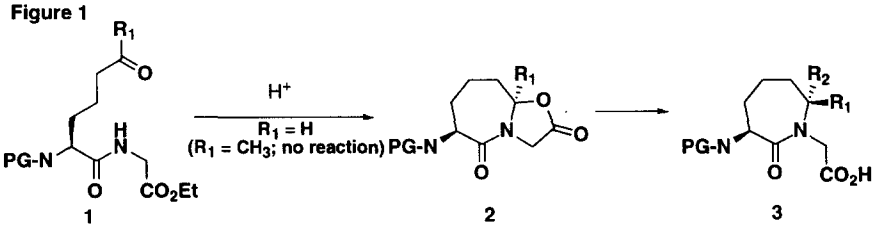
Abstract: Three diverse synthetic routes to C-7 dialkylated and spiro-alkylated azepinones are described. Compounds of this type may be used as conformationally restricted dipeptide surrogates. Additionally, the chiral synthesis of novel cyclopropanated lysine derivative **29** is demonstrated. Copyright © 1996 Elsevier Science Ltd

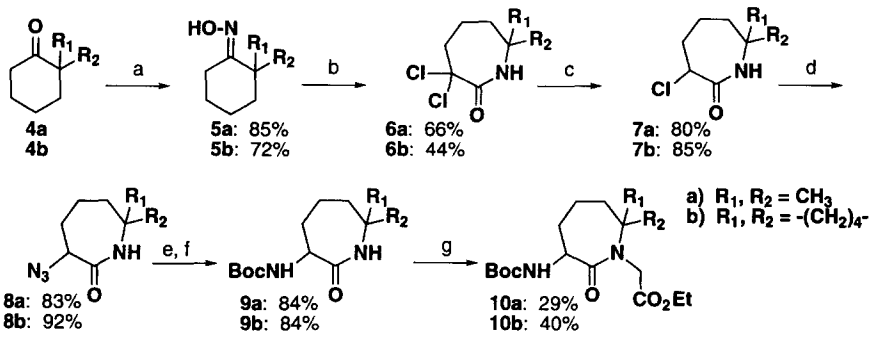
In a recent communication, we described a general method for the formation of C-7 substituted azepinones of structural type **3** where R_1 = H.[1a] Application of this methodology for the synthesis of C-7 di-substituted azepinones, starting with ketone **1** (R_1 = CH_3), failed due to the inability of this compound to undergo initial intramolecular acid catalyzed cyclization to give **2** or a variant thereof. Thus we sought to develop alternate routes to C-7 di-substituted azepinones related to **3** where R_1 and R_2 are both alkyl or joined to form a spirocyclic ring. Previous reports from this laboratory suggest that compounds of this type could be utilized as potential conformationally restricted dipeptide mimetics.[1b] We report here syntheses of N-methylcarboxy-3-amino-7,7-dialkyl-azepin-2-one intermediates related to **3**.

Figure 1



Our first approach involved a variation of the methodology developed by Sugg *et al.*[2] that provided the 7,7-dimethyl **10a** and spiro-cyclopentyl analog **10b** from cyclohexanones **4a** (R_1= R_2 = CH_3) and **4b** (R_1, R_2 = -$(CH_2)_4$-)[3] respectively (Scheme 1). Preparation of oximes **5a,b** under standard conditions followed by PCl_5-mediated Beckmann rearrangement provided dichloro-ε-lactams **6a,b**. Carefully controlled hydrogenolysis led to monochlorides **7a,b** and displacement with sodium azide gave **8a,b**. Catalytic reduction of the azides followed by treatment with Boc anhydride gave racemic **9a,b**. Alkylation[1c] of **9a,b** proved extremely difficult due to the steric influence of the neighboring geminal dimethyl/spirocyclopentyl group. Under forcing conditions (excess $LiN(TMS)_2$ and $BrCH_2CO_2Et$, THF, room temperature), **9** could be alkylated to give a mixture of mono and dialkylated products,[4] from which **10** could be isolated by column chromatography.

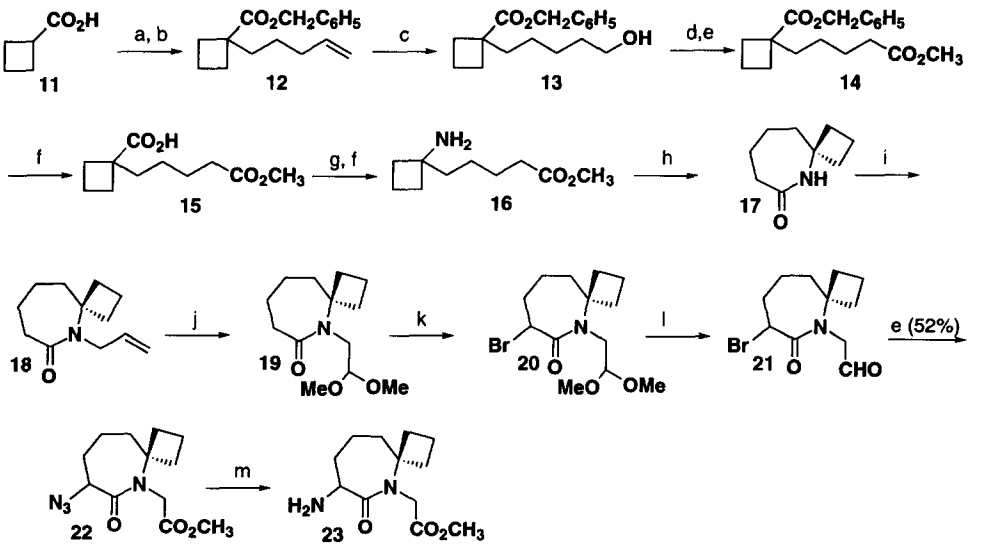
Scheme 1



a) NH_2OH•HCl, pyridine, EtOH b) PCl_5, Cl_2, CH_2Cl_2 c) H_2, 10% Pd/C, HOAc d) NaN_3, DMF, 50 °C e) H_2, 10% Pd/C, MeOH f) Boc_2O, Et_3N, $CHCl_3$ [from 8] g) $LiN(TMS)_2$, $BrCH_2CO_2Et$, THF

Because the corresponding spiro[3.5]nonanone was not conveniently available,[5,6] we decided to develop an alternate route to the spirocyclobutyl analog **23** (Scheme 2). We planned that alkylation of the dianion of cyclobutanecarboxylic acid, followed by functional group manipulation and lactamization, would provide an entry into this series. Thus, treatment of **11** with 2 equivalents of n-BuLi at 0 °C followed by reaction with excess 5-bromo-1-pentene and subsequent esterification led to **12** in high yield. Oxidative hydroboration of **12,** followed by Swern oxidation and treatment of the resulting crude aldehyde with bromine

Scheme 2



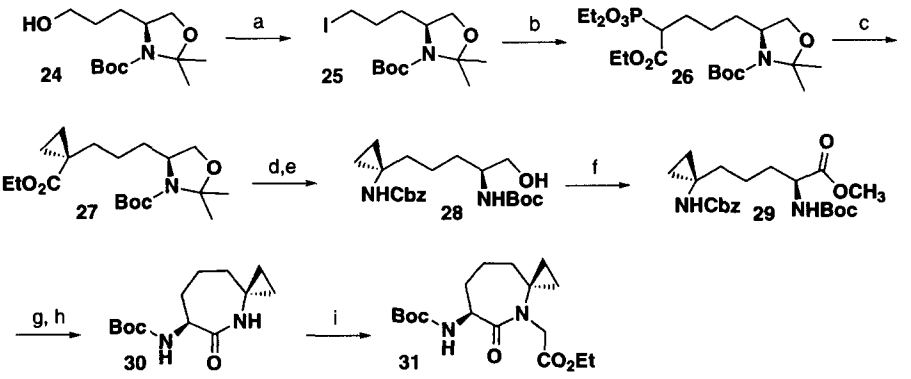
a) 2 LDA, THF, -78 °C then $Br(CH_2)_3CH=CH_2$ b) Cs_2CO_3, BnBr, DMF; 88% c) BH_3•THF, THF then NaOH, H_2O_2; 90% d) ClCOCOCl, DMSO, CH_2Cl_2 then Et_3N e) Br_2, aq. Na_2CO_3,MeOH; 80% f) H_2, $Pd(OH)_2$/C, EtOH; 100% g) 1. $ClCO_2Et$, Et_3N, THF. 2. NaN_3, acetone, H_2O. 3. toluene, reflux. 4. BnOH, TMSCl, CH_2Cl_2; 57% h) Me_3Al, CH_2Cl_2; 96% i) KOt-Bu, DMSO then $BrCH_2CH=CH_2$; 68% j) 1. O_3, CH_2Cl_2 then DMS. 2. p-TSA, $CH(OMe)_3$, MeOH; 47% k) LDA, THF, -78 °C then CBr_4; 84% l) 1. NaN_3, DMSO, 50 °C. 2. TFA, H_2O, CH_2Cl_2; 78% m) 10% Pd/C, MeOH; 95%.

in aqueous $NaHCO_3$/MeOH,[7] provided ester **14** in good yield. Hydrogenolysis gave half-ester **15** quantitatively. Compound **15** was converted to the corresponding acyl azide and subjected to Curtius rearrangement. To facilitate isolation and purification of the desired amine, the intermediate isocyanate was converted to the corresponding benzyl carbamate[8] and hydrogenolyzed to afford **16** in good overall yield.[9a]

Trimethylaluminum-mediated cyclization[1c] of amino-ester **16** proceeded smoothly to give lactam **17** in high yield. Our plan at this point was to append the desired acetate side chain to the lactam nitrogen and then functionalize at C-3 *via* a lithium dianion. While alkylation of **17** with $BrCH_2CO_2Et$ was successful ($LiN(TMS)_2$, THF, 70%), several attempts to form a dianion of the resulting lactam-ester failed. Deuterium oxide quenching experiments showed deuterium incorporation only at the methylene carbon of the ester. As a result, a functionalized side chain was required that would be innocuous to the anionic conditions necessary to substitute at the C-3 position of the lactam. Allylation of **17** (KOt-Bu/DMSO) gave N-allyl lactam **18**. Ozonolysis and acetalization provided acetal **19** which was subsequently metallated (LDA, -78 °C) and quenched with tetrabromomethane to give bromide **20** in excellent yield.[9b] Displacement of the bromide with sodium azide/DMSO and acidic work-up provided azido-aldehyde **21**. Oxidation of the aldehyde by bromine in aqueous methanol[7] gave methyl ester **22.** Subsequent hydrogenolysis gave the desired racemic spiro-fused lactam **23** in 15 steps and 7% overall yield from cyclobutanecarboxylic acid.

For the generation of the spirocyclopropane derivative **30** (Scheme 3), we applied the phosphonate-promoted cyclopropanation reaction reported by Petter *et al.*[10] Utilization of this methodology on a chiral precursor provided the protected dipeptide surrogate **31** in homochiral form. Numerous preliminary attempts to form the cyclopropane ring onto a properly modified glutamic acid residue failed. We attribute this to the incompatibility of the strongly basic cyclopropanating conditions with the α-ester functionality present in the protected glutamic acid. Reducing this functionality to the alcohol oxidation state (oxazolidine **24**) provided

Scheme 3



a) I_2, imidazole, Ph_3P, THF; 100% b) NaH, $(EtO)_2POCH_2CO_2Et$, DMF; 82% c) NaH, ethylene oxide, toluene, EtOH; 54% d) NaOH, H_2O, MeOH ; 100% e) 1. $ClCO_2Et$, Et_3N, THF. 2. NaN_3, acetone, H_2O. 3. toluene, reflux. 4. BnOH, TMSCl, CH_2Cl_2; 36% f) 1. ClCOCOCl, DMSO, CH_2Cl_2, -78 °C then TEA. 2. Br_2, aq. Na_2CO_3, MeOH; 47% g) HCO_2NH_4, 10% Pd/C, EtOH h) Me_3Al, CH_2Cl_2; 52% i) $LiN(TMS)_2$, THF then $BrCH_2CO_2Et$; 85%

the successful, if lengthy, synthesis. Thus, treatment of alcohol **24**[11] with iodine/triphenylphosphine afforded iodide **25** in quantitative yield. Reaction of this iodide with sodium triethyl phosphonoacetate gave **26**, which

was treated with sodium hydride and ethylene oxide to give cyclopropyl ester **27** in fair yield.[10] After saponification, the acid was subject to acyl azide formation, Curtius rearrangement, and carbamate formation as described for the cyclobutyl analog **15**. Acidic work-up provided the bis-carbamate alcohol **28** in 36% overall yield from **27**. The alcohol was oxidized to afford the orthogonally protected ω-cyclopropyl-L-lysine ester **29** that was subsequently subjected to hydrogenolysis and trimethylaluminum-catalyzed cyclization to give the desired spirolactam **30**. Lithium hexamethyldisilazide induced alkylation of **30** with ethyl bromoacetate proceeded in suprisingly high yield, as compared to its closely related dimethyl analog **9a**, to give **31**.[12] We attribute the difference in reactivity to the diminished steric interference of the cyclopropyl methylenes of **30** as compared to the unrestrained methyls of **9a**.

In summary, we have prepared four new 7,7-disubstituted-3-amino-azepin-2-ones, one of these in enantiomerically pure form, by several synthetically useful pathways. In addition, the first synthesis of **29**, an orthogonally protected cyclopropanated L-lysine derivative, was described. Further modification of the C-7 di-substituted azepinones and their incorporation in the design of dual metalloprotease inhibitors[1b] will be the subject of a future report.

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9. a) Preparation of **16**: To 11.35 g (53.0 mmol) of **15** in 100 mL of THF at 0 °C under nitrogen was added 7.8 mL (56 mmol) of triethylamine and then 5.2 mL (54.3 mmol) of ethyl chloroformate dropwise over 15 min. The temperature was not allowed to rise above 6 °C. The resulting thick slurry was stirred for 10 min and then treated rapidly with a slurry of 7.34 g (113 mmol) of sodium azide in 40 mL of 1:1 acetone/water. The solution thus formed was stirred for 15 min, diluted with 100 mL of ice water and extracted twice with 125 mL portions of toluene. The organic extracts were combined, washed once with 5% potassium hydrogen sulfate, once with brine, dried ($MgSO_4$) and filtered. The filtrate was set to reflux with the aid of a Dean-Stark trap: 175 mL of solvent was removed from the reaction. After 30 min, the residue was cooled to room temperature to provide nearly pure isocyanate (IR: 2240, 1735 cm^{-1}).

   The solution was diluted with 50 mL of dichloromethane under nitrogen at room temperature and treated with 8.2 mL (78 mmol) of benzyl alcohol and 0.4 mL (4.5 mmol) of chlorotrimethylsilane. After 40 min, the reaction was quenched with 5 mL of saturated sodium bicarbonate solution, partitioned, dried ($MgSO_4$) and evaporated. The resulting oil was dissolved in 100 mL of nitrogen-purged methanol, treated with 1.7 g of 20% palladium hydroxide-on-carbon and hydrogenated in a Parr hydrogenator for 16 h. The reaction mixture was purged with nitrogen, filtered and the filtrate evaporated. The residue was diluted with ether and extracted 3 x 50 mL 10% HCl. The acidic extracts were combined and washed three times with ether. The aqueous layer was made basic with KOH pellets to pH 8.5 and extracted twice with dichloromethane. The dichloromethane extracts were combined, dried (Na_2SO_4) and evaporated to provide essentially pure **16** as a colorless oil, 5.56 g, 57%.

   b) Preparation of **20**: To a solution of lithium diisopropylamide prepared from 0.56 mL (4.0 mmol) of diisopropyl amine and 1.60 mL (4.0 mmol, 2.5 M in hexanes) of n-butyllithium in 5 mL of THF at -78 °C was added a solution of 908 mg (3.76 mmol) of **19** in 4 mL of THF over 2 min. The reaction was warmed to -45 °C and stirred 45 min. To this pale yellow solution was added a solution of 1.37 g (4.11 mmol) of tetrabromomethane in 5 mL of THF over 15 min. The resulting deep red-brown solution was stirred for 20 min, quenched cold with saturated ammonium chloride solution and extracted twice with ethyl acetate. The extracts were combined, washed once with brine, dried (Na_2SO_4) and evaporated. Purification by flash chromatography (5 x 15 cm column, 3:7 ethyl acetate/hexanes) provided **20** as white solid, mp 62-64 °C, 1.012 g, 84% yield.
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12. Optical rotation for selected compounds: **25**, $[\alpha]_D$ = +17.6 ° (c = 1.25, $CHCl_3$); **26**, $[\alpha]_D$ = +20.5 ° (c = 1, $CHCl_3$); **27**, $[\alpha]_D$ = +20.7 ° (c = 1, $CHCl_3$); **28**, $[\alpha]_D$ = -5.4 ° (c = 1, $CHCl_3$); **29**, $[\alpha]_D$ = -14.5 ° (c = 0.75, $CHCl_3$); **31**, $[\alpha]_D$ = -23 ° (c = 0.75, $CHCl_3$).

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