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STEREOSPECIFIC SYNTHESES OF 3-SPIRO-EPOXYAZETIDIN-2-ONES

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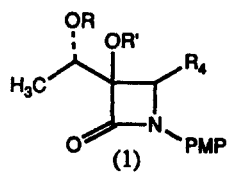
Abstract Isomerically pure 3-benzyloxy-3-hydroxyethylazetidin-2-ones, prepared by non-chelation controlled L-Selectride reduction of 3-acetyl-3-benzyloxyazetidin-2-ones, have been converted into the both possible 3-spiro-epoxyazetidin-2-ones.

During studies directed towards the stereospecific syntheses of various diastereoisomers of 3-hydroxyethyl-3-methoxyazetidin-2-ones(**1**,**R'=Me**) difficulties were encountered in carrying out efficient bimolecular nucleophilic substitution at the highly hindered hydroxyethyl group. The possibility of utilizing compounds such as (**1**, **R'= H**) as intermediates for the preparation of spiro-epoxides (**2**) via an internal nucleophilic substitution at either C-3 or the hydroxyethyl carbon was recognized. Since this unusual combination of functionalities is not well described, we would like to present our results in this area.[1,2]



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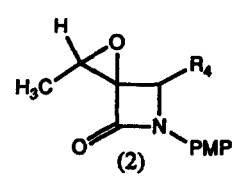
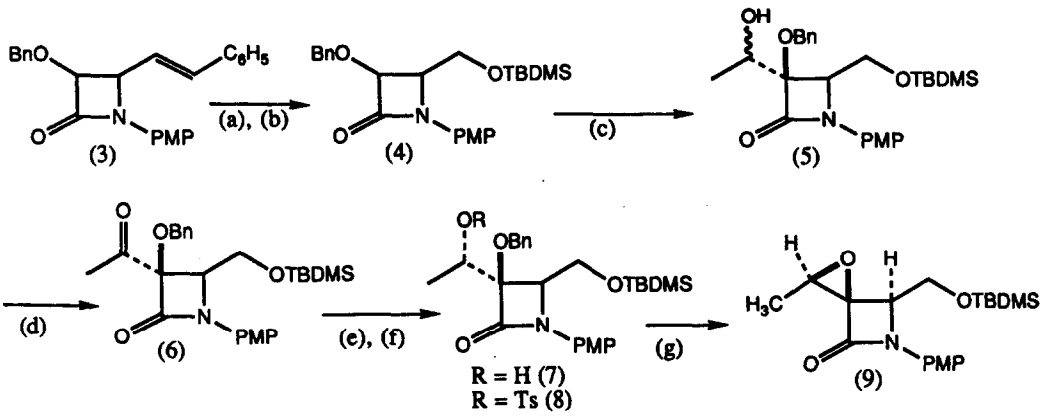


(2)

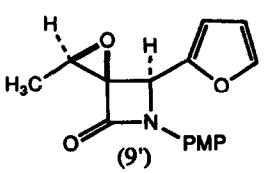
The 3-benzyloxyazetdinone (**3**)[3] (PMP = p-methoxyphenyl), prepared in 50% yield from benzyloxyacetyl chloride via a 2+2 cylcoaddition reaction with the imine derived from p-methoxyaniline and cinnamaldehyde, was converted into (**4**) using standard methodology. Lithiation of (**4**) using a slight excess of LDA at -78°C followed by reaction with acetaldehyde was highly diastereoselective and provided only two of the four possible diastereoisomers of (**5**) as an inseparable 1:1 mixture. Subsequent oxidation of the mixture with PCC provided a single acetyl compound (**6**) in ca. 60% overall yield of from (**4**).[2]

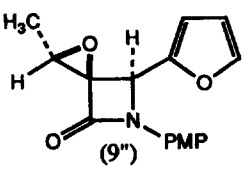
Reduction of (**6**) with 1.1 eq. of L-Selectride in the presence of 2.2 eq. of TMEDA in THF at -78°C gave the hydroxyethylazetidinone (**7**) in 75% yield as the sole reduction product as determined by 300 MHz NMR spectroscopy. The relative configuration of this compound has been confirmed by relating it to to a substance of known configuration.[4]



(a) O_3/O_2, -78°C, then $NaBH_4$ (b) 2,6-lutidine, TBDMS-triflate (55% overall), (c) LDA, THF, -78°C, then acetaldehyde (80%) (d) PCC, NaOAc, 4 A° mol. sieves (85%), (e) 1.1 eq. L-Selectride, 2.2 eq. TMEDA, THF, -78°C (75%), (f) NaH, DMF, tosylimidazole (75%), (g) ammonium formate, methanol, 5% Pd/C (80%)

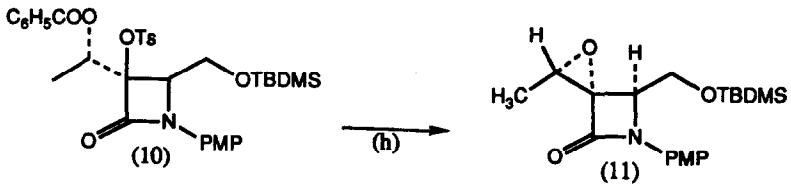
Conversion of (7) to (8) (δ= 5.1, q, J = 6.6 Hz for the CH of the hydroxyethyl group) was best carried out using NaH/tosylimidazole.[5] The debenzylation-oxirane formation sequence was conveniently performed as a single pot operation with ammonium formate, 5% Pd/C in refluxing methanol as the hydrogen transfer reagent combination.[6] The intermediate 3-hydroxyazetidinone was not isolated. The spiro-epoxide (9) {ir: 1765 cm^{-1}, nmr: δ = 7.5 (dd, 2 H, J= 2.2 Hz, J= 6.7 Hz) 6.8 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 4.3 (m,1 H), 3.9 (two m, 1 H), 3.7 (s, 3 H), 3.4 (q, 1 H, J= 5.2 Hz), 1.5 (d, 3 H, J= 5.2 Hz), 0.8 s, 9 H), (-)0.02 (s, 3 H), (-)0.04(s, 3 H) HRMS calcd for $C_{19}H_{29}NO_4Si$ 363.1906, found 363.1856}, the result of an inversion at the hydroxyethyl carbon atom, was isolated in 80% yield following column chromatography. The C-4 (2-furyl) analog (9') {ir: 1760 cm^{-1}, nmr; δ= 7.4-6.4 (series of m, 7 H), 5.1 (s, 1 H), 4.2(q, 1 H, J = 6.4 Hz), 3.8 (s, 3 H), 1.3 (d, 3 H, J = 6.4 Hz} was similarly prepared in 50% yield from the corresponding tosylate. In the furyl series, subjecting a ca.1:1 mixture of starting hydroxyethylazetidinones (diastereoisomeric at the hydroxyethyl group) to the sequence outlined above led to the formation of ca.1:1 diastereoisomeric mixture of spiro-epoxides{(9') and (9")}.





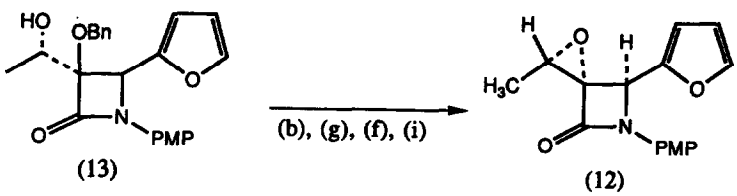
Preparation of the epoxide (11), epimeric to (9) also commenced with alcohol (7). Benzoylation using NaH/benzoylimidazole,[7] subsequent hydrogen transfer

debenzylation and formation of the tertiary tosylate (NaH/ tosylimidazole) furnished (**10**) in 75% yield from (**7**). Exposure of (**10**) to 1.1 eq. of sodium methoxide in a CH_3OH-THF mixture led to the formation of oxirane (**11**) {ir: 1770 cm^{-1}; nmr: δ =7.3 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 6.8 (dd, 2 H, J= 2.2 Hz, J= 6.8 Hz), 4.2 (t, 1 H, J= 2.9 Hz), 4.0 (dd, 1 H, J= 2.9 Hz, J= 11.8 Hz), 3.7 (m, 4 H), 3.4 (q, 1 H, J= 5.2 Hz), 1.5 (d, 3 H, J= 5.2 Hz), 0.77 (s, 9 H), 0.0(6H s). HRMS calc for $C_{19}H_{29}NO_4Si$ 363.1906, found 363.1910} in 65% yield.



(h) 1.1 eq. NaOMe, methanol-THF, R.T. (65%).

For preparation of the C-4 (2-furyl) analog (**12**) {ir: 1770 cm^{-1}; nmr: δ = 7.3-6.3 (series of m, 7 H), 5.19 (s, 1 H), 3.7 (s, 3 H), 3.2 (q, 1 H, J=5.0 Hz), 1.5 (d, 3 H, J= 5.0 Hz). HRMS calc for $C_{16}H_{15}NO_4$ 285.1023, found 285.1037} the secondary hydroxyl group in (**13**) was protected as its TBDMS ether. The epoxide formation step involved reaction of the tertiary tosylate, prepared by debenzylation of the silylated alcohol followed by tosylation, with 2.2 eq. of TBAF in THF. The yield for the last step was 64%.



(i) 2.2 eq. TBAF, THF, R.T. (64%). Other steps as indicated above.

Use of a 1:1 mixture of the diastereoisomeric alcohols instead of (**13**) (diastereoisomeric at the hydroxyethyl group) as the starting material, gave a 1:1 mixture of (**12**) and (**14**) {not shown} in comparable yield. Thus all four diastereomers of the spiro-epoxide (**2**) are accessible by the series of reaction outlined above.[8]

The spiro-epoxides synthesized show good chromatographic and thermal stability. These compounds show a surprisingly high IR stretching frequency (1770-1765 cm^{-1}) for the carbonyl group. This can be attributed to the presence of an electron withdrawing oxygen substitutent at C-3 coupled with the strain introduced by

formation of the spiro-epoxide system. The possibility that this higher β-lactam strain may be reflected in the biological activity of bicyclic derivatives of (9) and (11) e.g.thienamycin analogs is being investigated.[10]

Conclusion: By combining the diastereospecific reduction of acylazetidinones such as (5) and the suitable functional group manipulations, it has been possible to synthesize the title compounds in a diastereospecific manner.

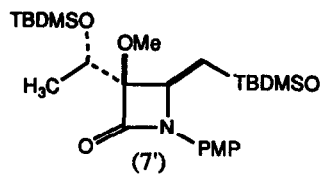
References and Notes

(1) [a] Sebti, S.; Fouccaud, A. *Tetrahedron* **1984**, *40*, 3233. [b] John, D.I.; Jephcote, V.J.; Edwards, P.D.; Luk, K.; Williams, D.H. *Tetrahedron Lett.* **1984**, *25*, 2915.

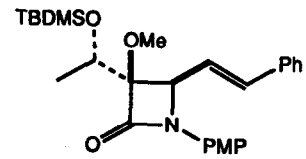
(2) These observations are similar to those in the case of 3-methoxyazetidinones. Results pertaining to those studies have been submitted for publication elsewhere.

(3) All compounds involved in these studies were racemic mixtures. All intermediate azetidinones showed spectral properties in agreement with the assigned structures.

(4) By a series of straightforward transformations (7) was converted into 3-methoxyazetidinone (7'). The same compound was obtained from the C-4 cinnamylazetidinone, the stereochemistry of latter has been established by X-ray diffraction analysis.[2]



(7')



(5) Fraser-Reid, B.; Hicks, D.R. *Synthesis* **1974**, 203.

(6) Beig, T.; Szeja, W. *Synthesis* **1985**, 75. Formate salts as hydrogen transfer reagents Ram, S.; Erhankaufer, R.E. *Synthesis* **1988**, 91.

(7) Hodgson, K.; Carey, F.A. *Carbo. Res.* **1970(12)**, 463.

(8) Epoxide formation via displacement of a leaving group at a tertiary centre are well known to be facile in simple systems such as 3-chloro-3-methyl-butan-2-ol.9Such displacements are often accompanied by carbonyl compounds resulting from a 1,2 hydride or alkyl group shift.[9] It may be argued that the formation of epoxide from the tertiary tosylates may proceed through the formation of the corresponding tertiary carbonium ion.[10] Even if such a process plays a part in oxirane formation process, the attack of the internal nucleophile (the secondary hydroxyl group) will take place on the side *opposite* to the larger substituent at C-4. Both of these will result in overall inversion of configuration at the carbon atom in question.

(9) Streitwieser A.J. Jr. Chem Rev. **1956**, *56*, 571

(10) Carbonium ions bearing an electron withdrawing group (such as keto or cyano) are known: Creary, X. *Acc. Chem. Res.* **1985**, *18*, 3.

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