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# Synthesis of a [2]benzazepine analogue of clavizepine

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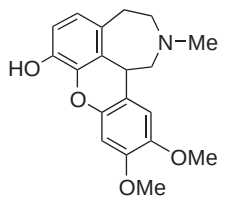
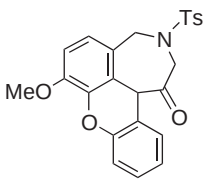
**Abstract**—The synthesis of *N*-tosylbenzopyran[2]benzazepinone **2** using a simple protocol for assembly of an azepine ring on the xanthene skeleton is described. Formation of the C–C bond between C9 of the xanthen-9-ol **7** and the β-C of *N*-tosyl aminoacetaldehyde dimethyl acetal leads to **10**, which upon treatment with formaldehyde undergoes ring closure. 

Clavizepine (**1**), first isolated from the plant *Corydalis claviculata* (L.) DC.,[1] is the sole member of the benzopyran[3]benzazepine class of alkaloids. Its total synthesis has been achieved by Ikeda and co-workers[2a,b] and in our own laboratory.[2c,d] In the course of pharmacological evaluation of some clavizepine analogues we discovered that certain *N*-tosylated clavizepine precursors have interesting biological properties. In view of these findings, we decided to investigate modified analogues with the structure of *N*-tosylbenzazepines, starting with the [2]benzazepine **2**.



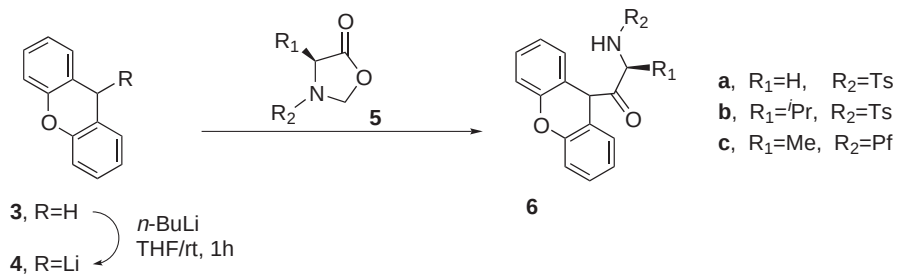

**Clavizepine (1)**




**2**

Initially, we designed a synthetic strategy based on acylation of a 9-xanthenyllithium with an appropriate amino acid derivative as the source for the $C_2N$ unit, which could then be cyclised to the required azepine (Scheme 1).

To this end we prepared the *N*-tosyloxazolidinone derivatives of glycine and L-valine **5a** and **5b** by *N*-tosylation of the corresponding amino acids (1 M NaOH, TsCl, rt, 4.5 h) followed by treatment with excess paraformaldehyde and catalytic *p*-toluenesulfonic acid in refluxing benzene, with azeotropic removal of water. However, addition of a THF solution of either of these oxazolidinones to 9-xanthenyllithium (**4**) at −100, −78 or 0°C failed to afford the corresponding acylated products (**6a** or **6b**). Instead, the main product was the xanthene **3**, which was probably the result of protonation of **4** by the acidic α-hydrogens of the starting oxazolidinones. To avoid this undesired process we tried replacing the *N*-protecting group with the more




**Scheme 1.**

*Keywords*: xanthenes; acetals; amino aldehydes; benzazepines; polycyclic heterocyclic compounds.
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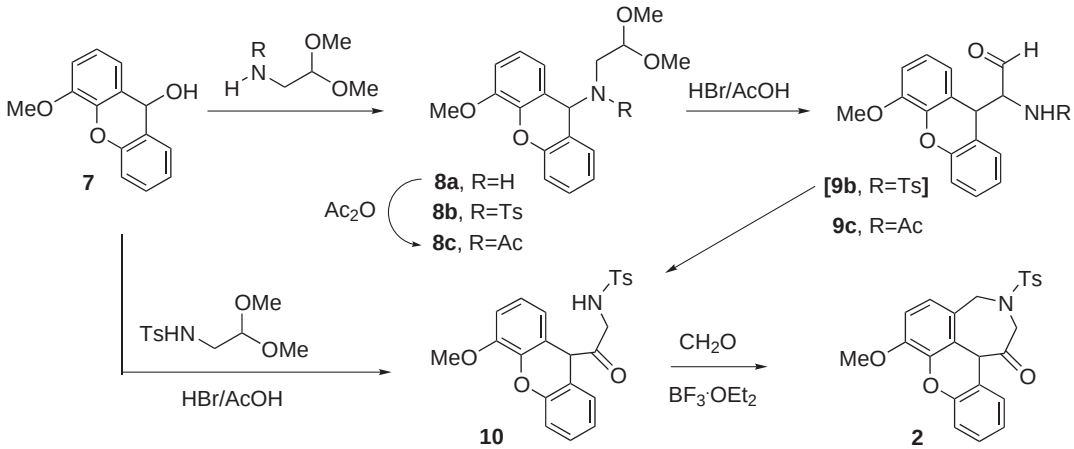


**Scheme 2.**

sterically hindered and less electron withdrawing 9-phenylfluoren-9-yl group (Pf), first used by Rapoport to protect α-amino carbonyl compounds against enolisation.[3,4] When a THF solution of the oxazolidinone **5c**, prepared from L-alanine following a reported procedure,[4b] was cooled to −78°C and treated with xanthenyllithium **4**, a 43% yield of the expected acylation product **6c** was obtained.

However, at this point, while working on a parallel project, we discovered an alternative, much simpler and more direct route to the desired methoxy substituted amino ketone **10** (Scheme 2). Specifically, we found that the *N*-tosyl derivative **8b**,[5] which is readily prepared from 4-methoxyxanthen-9-ol (**7**),[6] afforded compound **10** directly in 50% yield when treated with HBr in acetic acid at rt.[7] A plausible mechanism consists of attack by the enolic form of the hydrolysed acetal derivative of **8** on the doubly benzylic, highly activated position 9 of the xanthene to give the amino acetaldehyde **9b**, which in the reaction conditions used might undergo a 1,2-(xanthen-9-yl) shift followed by a 1,2-hydrogen shift to give **10** according with an unusual rearrangement already described.[8] In support of this mechanism, the *N*-acetyl analogue **8c**[9] was converted to the amino aldehyde **9c**; this compound, however, unexpectedly failed to rearrange to the corresponding amino ketone, being stable under the HBr/AcOH conditions employed.

The above mechanistic hypothesis suggested an even more direct way of getting the required amino ketone **10**, namely by intermolecular reaction of xanthen-9-ol **7** with *N*-tosyl aminoacetaldehyde dimethyl acetal under the same acidic conditions as in the intramolecular case. This procedure led to an improved 64% yield of **10** after chromatographic purification.[7,10]

Finally, reaction of **10** in chloroform with 37% aq. formaldehyde in the presence of boron trifluoride diethyl etherate afforded a 90% yield of [2]benzazepinone **2**.[7,11] In this way, we constructed the *N*-tosyl-[2]benzazepinone analogue of clavizepine in two steps from readily available materials. Further application of this methodology to related systems is currently being investigated.

## Acknowledgements

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4. (a) *N*-Pf-oxazolidinones derived from amino acids have previously been used in our laboratory for the intramolecular acylation of aryllithium derivatives: Paleo, M. R.; Castedo, L.; Domínguez, D. *J. Org. Chem*. **1993**, *58*, 2763–2767; (b) More recently, intermolecular reactions with Li and Mg organometallics have been described: Paleo, M. R.; Calaza, M. I.; Sardina, F. J. *J. Org. Chem*. **1997**, *62*, 6862–6869.
5. Solid **7** (1.0 g, 4.38 mmol) was added in small portions, with stirring at rt, to a solution of thionyl chloride (0.40 ml, 5.48 mmol) in 15 ml of dry hexane and the mixture was refluxed under anhydrous conditions ($CaCl_2$ tube) for 30 min. After cooling in an ice-bath, the solvent was decanted off and the solid residue was washed twice with dry hexane, dried under vacuum, and dissolved in 10 ml of dry THF. This solution was added through a cannula to a solution of the sodium salt of *N*-tosyl amino-

acetaldehyde dimethyl acetal in 10 ml of THF, and the resulting mixture was refluxed for 3 h. The solvent was then evaporated and the residue partitioned between EtOAc and water. After evaporation of EtOAc the residue was crystallised from $Et_2O$–hexane affording 0.62 g (30%) of **8b**. Mp 114–117°C. $^1$H NMR $\delta$ 7.91 (d, $J=8$, 2H), 7.39 (d, $J=8$, 2H), 7.28–7.14 (m, 3H), 7.03–6.84 (m, 3H), 6.66 (dd, $J=7.5$ and 1.5, 1H), 6.43 (1H, s), 3.92 (s, 3H), 3.67 (t, $J=5.0$, 1H), 3.04–2.98 (m, 2H), 2.92 (s, 3H), 2.89 (s, 3H), 2.49 (s, 3H).

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7. All new compounds were fully characterised spectroscopically and had satisfactory elemental analyses or HRMS data.
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9. Acetal **8c** was prepared by acetylation of **8a** ($Ac_2O$, THF, $K_2CO_3$, −20°C, 12 h), which was obtained from xanthen-9-ol **7** by condensation with aminoacetaldehyde dimethyl acetal (100 mol%) in refluxing toluene containing AcOH (30 mol%).
10. Commercial 33% HBr in AcOH (3ml) was added dropwise at rt to a solution of xanthen-9-ol **7** (0.5 g, 2.19 mmol) and *N*-tosyl aminoacetaldehyde dimethyl acetal (0.75 g, 2.80 mmol) in 1.5 ml of glacial acetic acid. The resulting mixture was stirred for 0.5 h and then poured onto water and extracted with EtOAc. After evaporation of the organic solvent the residue was chromatographed on an $SiO_2$ column (30/70, EtOAc/hexane), affording 0.60 g (64%) of **10** as an oil. $^1$H NMR $\delta$ 7.48 (d, $J=8.5$, 2H), 7.31–6.89 (m, 8H), 6.58 (dd, $J=7.5$ and 2, 1H), 5.11 (t, $J=5.5$, 1H), 4.90 (s, 1H), 3.96 (s, 3H), 3.69 (d, $J=5.5$, 2H), 2.39 (s, 3H).
11. To a solution of **10** (1.0 g, 2.36 mmol) in 35 ml of dry chloroform at 0°C under Ar were added 37% aq. formaldehyde (0.26 ml) and $BF_3{\cdot}OEt_2$ (1.26 ml, 7.50 mmol). After stirring for 90 min, the reaction mixture was poured onto water and basified with 10% $NH_4OH$. The organic phase was concentrated and purified on a silica gel column eluted with methylene chloride, affording 0.91 g (90%) of **2** as a white solid. Mp 205°C (decomp.). $^1$H NMR $\delta$ 7.79 (d, $J=8$, 2H), 7.41 (d, $J=8$, 2H), 7.29 (td, $J=8.3$ and 1.2, 1H), 7.17 (dd, $J=8.5$ and 1.2, 1H), 7.07 (td, $J=7.5$ and 1.5, 1H), 6.87 (d, $J=8.5$, 1H), 6.81 (d, $J=8.5$, 1H), 6.68 (dd, $J=7.5$ and 1, 1H), 5.15 (s, 1H), 5.11 (d, $J=14.5$, 1H), 4.44 (d, $J=18.5$, 1H), 4.40 (d, $J=14.5$, 1H), 3.90 (s, 3H), 3.73 (d, $J=18.5$, 1H), 2.49 (s, 3H). $^{13}$C NMR $\delta$ 201.9 (CO), 150.8, 148.6, 144.7, 141.1, 135.4, 130.6 (3×CH), 129.6 (CH), 127.6 (2×CH), 124.0, 123.7 (CH), 123.6 (CH), 117.0 (CH), 116.4, 115.4, 111.6 (CH), 56.6 ($OCH_3$), 53.4 ($CH_2$), 51.6 ($CH_2$), 46.9 (CH), 21.9 ($CH_3$). IR (KBr): 1734 $cm^{-1}$. MS FAB 436 (M+1, 8%), 435 (7%), 404 (2%), 348 (6%). HRMS (FAB): calcd: 436.1219; found: 436.1215.