Enantioselective Synthesis of a 2,3,4-Trisubstituted Pyrrolidine from 1-Hydroxymethyl-4-phenylsulfonylbutadiene

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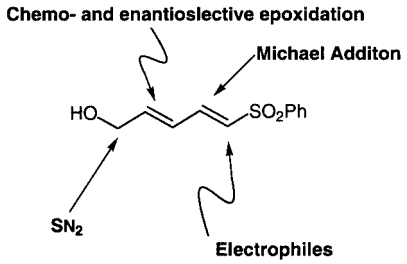
Abstract: A chiral 2,3,4-trisubstituted pyrrolidine glycosidase inhibitor has been obtained from 1-hydroxymethyl-4-sulfonylbutadiene.

Key words: enantioselective synthesis, pyrrolidines, sulfonylbutadienes

As part of a program seeking to exploit the reactivity of 1-hydroxymethyl-4-sulfonylbutadienes in the synthesis of oxygen and nitrogen heterocycles we have prepared a chiral 2,3,4-trisubstituted pyrrolidine, **9**, recently synthesized by several groups for its glycosidase inhibitor activity.[1]

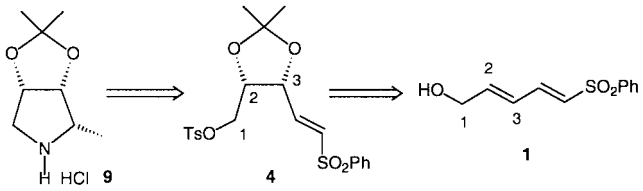
1,3-dienes with a sulfone or sulfoxide group have been the object of study of many research groups in recent years.[2] In our case we want to exploit the presence of an allylic alcohol that opens the door to enantioselective syntheses.

The versatility of this kind of compound is illustrated in Scheme 1.



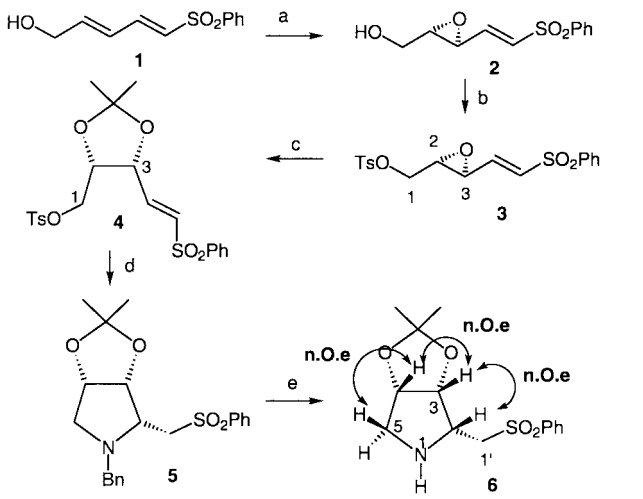
Scheme 1

In previous work we have reported the synthesis of isosorbide analogues that exploit the chemo- and enantioselective epoxidation of a sulfonylbutadiene and the reactivity towards electrophiles of the α position of the resultant vinyl sulfone.[3] In the work reported in this paper we wished to investigate the possibility of performing, in a one pot reaction, an S_{N2} displacement at an appropriately activated hydroxymethyl group and a Michael addition to the vinyl sulfone. With a nitrogen nucleophile, this methodology was expected to give pyrrolidines in chiral form, the enantiomer being accessed depending upon the Sharpless conditions. The presence of these pyrrolidines in natural and pharmaceutical products with interesting biological activities,[1,4] and their use as conformationally constrained amino acid analogues[4b], makes them interesting targets, and this procedure provides a versatile method for their synthesis. The retrosynthetic analysis for **9** is shown in Scheme 2.



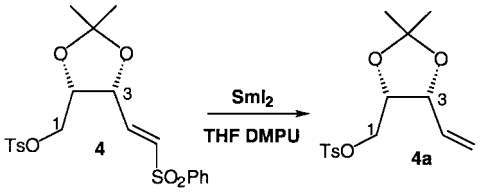
Scheme 2

As can be appreciated, the *trans* stereochemistry in the Δ^2 double bond of **1** will lead to the *trans* epoxide and thus frustrate any attempt at direct cyclization of **2** or derivatives such as **3**. It is necessary to change this configuration in order to produce the required ring. This was done by the Wershofen-Scharf procedure[5] – treatment of the tosyl epoxide **3** with $AlCl_3$ in acetone – which in one step gave the required stereochemistry and protection of the two hydroxy groups (Scheme 3).



Scheme 3 a) Sharpless, L(+)-DET, 85%; b) TsCl, Py., 80%; c) $AlCl_3$, acetone, 65%; d) $BnNH_2$, MeOH, Et_3N, 78%; e) H_2, Pd/C, MeOH, 95%

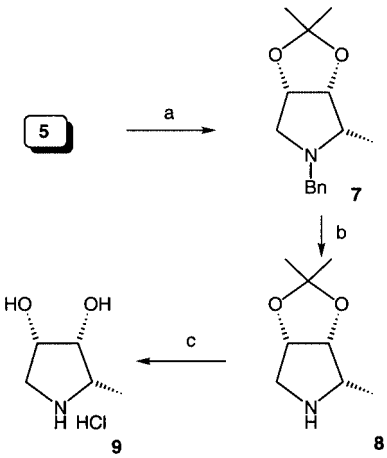
Treatment of **1**, under Sharpless conditions with L(+)-DET gave epoxide **2** in an excellent 98% e.e. and 85% yield. The enantiomeric excess was determined by ^{1}H NMR after preparation of the Mosher's ester of **2** and the Mosher's ester[6] of the racemic epoxide obtained by reaction with *m*-CPBA. A totally chemoselective epoxidation of the Δ^2 double bond is observed in this reaction. Once obtained, (–)-**2** was treated with *p*-TsCl in pyridine giving the tosylate **3** in an 80% yield. Reaction of **3** with $AlCl_3$ in acetone led to **4** in a moderate 65% yield with retention of the configuration at C-2 and inversion at C-3. In order to check the above stereochemical assignment, compound **4** was submitted to a desulfonylation[7] with samarium iodide (Scheme 4) to give compound **4a,** which has been obtained previously from ribonolactone.[5b]



Scheme 4

As can be seen **4** is an excellent intermediate for cyclization to produce diversely substituted pyrrolidines and other heterocycles. As we had expected, treatment of **4** with benzylamine gave **5** in 78% yield in a one pot reaction, no other diastereoisomer being detectable from the reaction. Finally, selective deprotection with H_2, Pd/C led to **6** in 95% yield.[8] The stereochemistry was assigned by a study of the ^{1}H NMR spectra and n.O.e experiments (Scheme 3).

Due to problems associated with desulfonylation of **6** which proceeded in low yield, it was decided to change the order of events for the synthesis of **9** (Scheme 5).



Scheme 5 a) Na(Hg), MeOH, 77%; b) H_2, Pd/C, MeOH, 90%; c) HCl 6 M, MeOH, 80%

Treatment of **5** with sodium amalgam under the usual conditions[2a] produced **7** in 77% yield. Debenzylation under the same conditions as before led to **8**, which was submitted without purification to treatment with 6 M HCl to give pyrrolidine **9** in an excellent 80% yield as its hydrochloride salt. This compound showed the same physical properties[9] as described in the literature.[1c]

Thus, we have obtained a chiral pyrrolidine, not only opening the way for the total synthesis of a variety of natural alkaloids,[10] but also using 1-hydroxymethyl-4-sulfonylbutadiene in an expeditious way that demonstrates the versatility of this compound.

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References and Notes

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(6) Preparation of the (*R*)-MPTA ester derivative and subsequent N.M.R. analysis at 400 MHz showed the optical purity to be 95%ee. See: Dale, J. A.; Dull, D. L. and Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543.

(7) D.e 93% by comparison with **4a** in reference 5b $[\alpha]_D^{21}$ = -44.5 (c 1.87, $CHCl_3$); Keck, G. E.; Savin, K. A. and Weglarz, M. A. *J. Org. Chem*. **1995**, *60*, 3194

(8) Selected data for compound **6**: $[\alpha]_D^{20}$ = +25.8 (c 0.10, $CHCl_3$); IR (film) ν (cm^{-1}) 3000, 2936, 1447, 1381, 1308, 1148, 1086, 650; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.95-7.50 (5H, m, -SO_2Ph), 4.67 (1H, dd, J = 5.3 and 4.0 Hz, H-4), 4.54 (1H, dd, J = 5.3 and 4.2 Hz, H-3), 3.57 (1H, dd, J = 14.0 and 5.0 Hz, Ha-1'), 3.36 (1H, dd, J = 14.0 and 7.0 Hz, Hb-1'), 3.22 (1H, m, H-2), 3.13 (1H, d, J = 12.7 Hz, Hα-5), 2.69 (1H, dd, J = 12.7 and 4.0 Hz, Hβ-5), 2.20 (1H, m, H-1), 1.41 (3H, s, Me-acetonide), 1.25 (3H, s, Me-acetonide). ^{13}C NMR ($CDCl_3$, 50.3 MHz). 139.7 (C-*ipso*), 133.7 (CH-*para*), 129.2 (2CH-*meta*), 127.2 (2CH-*ortho*), 111.1 (C-acetonide), 81.0 (CH-3), 80.8 (CH-4), 57.1 (CH-2), 55.9 (CH_2-1'), 52.6 (CH_2-5), 25.7 (Me-acetonide), 24.0 (Me-acetonide); m/z (FAB) 282, 154, 136, 107, 80. HRMS (FAB) m/z calc for $C_{14}H_{20}NO_4S$ 298.1113 found 298.1128

(9) Selected data for compound **9**: Colorless crystals, mp = 168-170 ºC (*i*-PrOH), $[\alpha]_D^{20}$ = -2.5 (c 1.00, H_2O), $[\alpha]_D^{20}$ = +2.4 (c 0.83, MeOH); literature values $[\alpha]_D^{20}$ = -3.0 (c 0.50, H_2O), personal communication A. Defoin. The optical rotation reported for this compound as hydrobromide salt is $[\alpha]_D^{20}$ = +3.2 (c 0.57, MeOH); [Lars Bierer, Dissertation, Universität Stuttgart 1999, p. 171]. NMR data are identical to those of litt. reference1c.

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