A new strategy for the elaboration of pyrrolidine *N*-oxides using the reverse-Cope elimination

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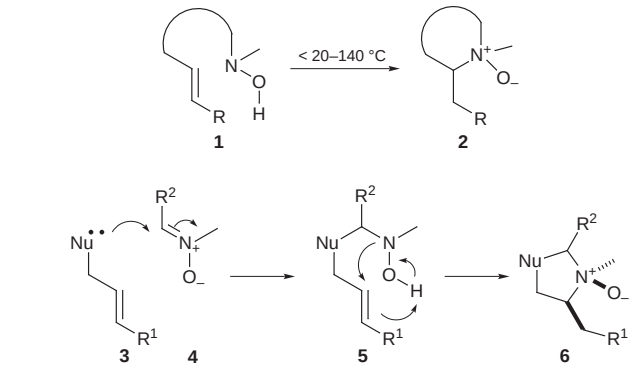
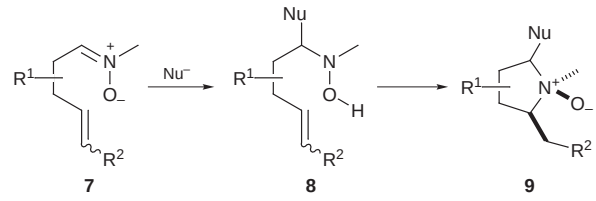
Condensations of the unsaturated nitrones 13 with lithiated methyl phenyl sulfone provide excellent yields of the unsaturated hydroxylamines 14 as single stereoisomers, which undergo rapid reverse-Cope elimination at ambient temperature, assisted by the constraint of the acetonide ring, leading to the pyrrolidine *N*-oxides 15 as single enantiomers.

As its name suggests, the reverse-Cope elimination is a reaction wherein a hydroxylamine and an alkene contained within the same molecule **1** undergo an addition reaction to give a cyclic *N*-oxide **2**. Originally discovered by the groups of House,[1] Black[2] and Oppolzer,[3] it is only relatively recently that the method has come to prominence, particularly due to the pioneering studies of Ciganek[4] who defined much of its scope and limitations as a useful approach to pyrrolidine *N*-oxides. Despite some earlier speculation,[1] results reported in a seminal paper by Oppolzer's group[5] provide excellent evidence that the transformation is a thermal pericyclic process related to the ene reaction. Subsequently, the latter group applied the reaction as a key step in a synthesis of the alkaloids lycorane and trianthine;[5] other neat applications by the Holmes group have further served to demonstrate the synthetic potential of the reverse-Cope process in the formation of pyrrolidines and also of cyclic nitrones, by related intramolecular additions of hydroxylamines to acetylene groups.[6] Our own contributions (Scheme 1) to this area have been centred around the use of condensation reactions between various unsaturated nucleophiles **3** and aldonitrones **4** to generate suitable hydroxylamines **5** which then undergo the reverse-Cope reaction to give a variety of five-membered heterocycles **6** [Nu = NMe, S, $PhSO_2CH$] and derivatives thereof.[7] With a view to extending the flexibility of the latter pyrrolidine *N*-oxide synthesis, we wondered whether suitable unsaturated hydroxylamines **8** could be generated by nucleophilic additions to molecules **7** containing both nitrone and alkene functions, with the idea of obtaining *N*-oxides **9** (Scheme 2). This idea also gave us an opportunity to test another speculation regarding the reverse-Cope elimination: would the rate of the reaction be increased if the two



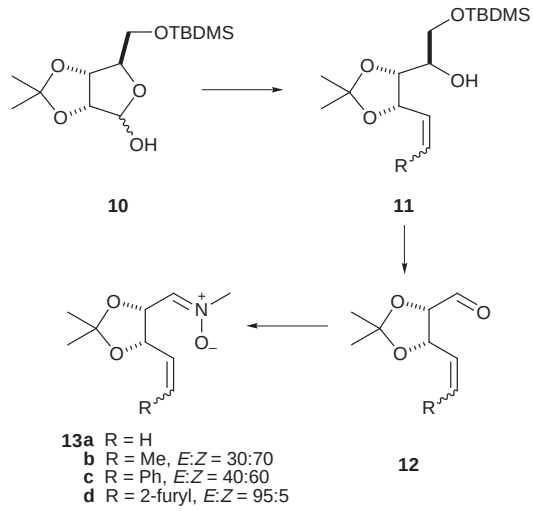
Scheme 1



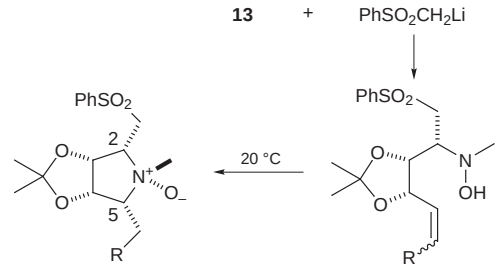
Scheme 2

reacting groups were held together by a second ring? In general, when a substituent is present on the terminus of the alkene group [*i.e.* **7**: $R^2 \neq H$], the rate of the reaction is slowed substantially, which can be a serious constraint when the sensitivity of the product precludes significant heating to induce cyclisation.[2,7] Ciganek in particular[4] has demonstrated the value of remote geminal substituents in aiding reverse-Cope cyclisations, presumably by a Thorp–Ingold effect, and we therefore felt that incorporation of a second ring would prove at least as effective. Herein, we report our first experiments in this area which have resulted in a new and highly stereoselective approach to pyrrolidine *N*-oxides and a somewhat unexpected stereochemical outcome.

We reasoned that an ideal starting material to test these ideas was D-ribose; protection of the primary hydroxy group as a silyl ether and acetonide formation[8] provided derivative **10** in which the acetonide ring provided the required constraint and the residual functionality the opportunity to incorporate the nitrone and alkene groups (Scheme 3). Subsequent Wittig homologation, crucially using potassium *tert*-butoxide as the base, led to good yields of the alkenes **11**, with the *E*/*Z* ratios shown. As the distal stereocentre would be removed if the reverse-Cope cyclisations were to be successful, we made no attempt to separate these isomers. Desilylation and diol cleavage then delivered the aldehydes **12** which were smoothly converted into the corresponding nitrones **13** under standard conditions.



Scheme 3



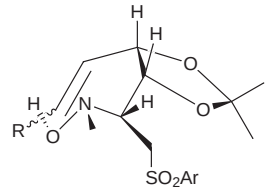
15a R = H, 1 h, 83%
b R = Me, 1 h, 83%
c R = Ph, 5 h, 65%
d R = 2-furyl, 2 h, 88%

Scheme 4

Addition of lithiated methyl phenyl sulfone (Scheme 4) to the nitrones **13** at −78 °C in THF, followed by warming to ambient temperature, quenching with aq. NH_4Cl and extractive work-up, delivered the expected[7] hydroxylamines **14**, essentially as single stereoisomers, according to ^1H and ^{13}C NMR analyses. At this stage, we did not know the configuration of the newly created stereocentre, although comparative spectroscopic data not unreasonably indicated that this was the same sense in each example. However, we suspected that the isomers shown (**14**) were formed, based on the work of the Dondoni group and the associated Houk model for such additions.[9] Further meaningful measurements was precluded when we were pleased to observe that the desired reverse-Cope elimination was already taking place as these analyses were being carried out. As indicated in Scheme 4, the cyclisations proceeded to completion remarkably quickly at ambient temperature in $CHCl_3$ solution, the slowest being the phenyl substituted analogue **14c** which, even so, only required 5 h. The final products **15** were purified by rapid column chromatography; following a brief elution with 5% MeOH–CH_2Cl_2, the rather polar *N*-oxides **15** were eluted as pure compounds using neat MeOH in the isolated yields shown (Scheme 4).

Each product was isolated as a single enantiomer, according to ^1H and ^{13}C NMR data. Detailed NMR analysis, in particular NOE measurements,[10] supported the all-*cis* structures **15** shown and was also consistent with the Dondoni–Houk conclusions concerning the initial carbanion addition.[9] This, perhaps at first, surprising result can be explained by the transition state conformation **16** wherein the alkene and hydroxylamine functions can line up in such a way as to allow for maximum orbital overlap, as indicated in the alternative view **17**. Molecular models indicate that such overlap is less favourable in the alternative chair-like conformation; attempts to quantify this argument are in progress. Such a transition state conformation is similar to one we have previously deduced to explain the stereochemical outcome of the reverse-Cope cyclisations summarized in Scheme 1.[7]

The remarkable ease with which the present cyclisations occur, presumably due to the additional ring constraint, together with the fact that this allows for the incorporation of additional functionality, suggests that this route should find many applications in the stereoselective synthesis of highly substituted pyrrolidines and derivatives thereof, in particular, the more difficult to obtain all-*cis* isomers. Studies aimed at exploiting this are in progress.



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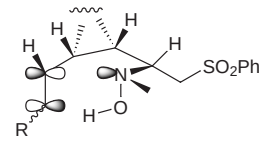

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Notes and References

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10 *Selected data* for **15a**: $[\alpha]_D^{20}$ +16.1 (*c* 0.51, CH_2Cl_2), $\delta_H(CDCl_3)$ 1.18 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.48, (3H, d, *J* 6.5, 5-CH_3), 2.95 (3H, s, N-CH_3), 3.25 (1H, dq, *J* 6.5 and 6.5, 5-H), 3.52 (1H, dd, *J* 15.0 and 6.5, CH_aH$_b$SO$_2$), 3.85 (1H, ddd, *J* 9.0, 6.5 and 4.0, 2-H), 4.05 (1H, dd, *J* 15.0 and 4.0, CH$_a$*H*$_b$SO$_2$), 4.50 (2H, m, 3- and 4-H), 7.35–7.50 (3H, m, ArH) and 7.80 (2H, m, ArH); $\delta_C(CDCl_3)$ 11.4 (5-CH_3), 25.1 (CH_3), 27.4 (CH_3), 53.1 (N-CH_3), 55.0 (CH_2SO_2), 77.0 (2-CH), 78.4 (5-CH), 83.1 [3(4)-CH], 83.4 [4(3)-CH], 115.5 (OCO), 128.6 and 129.8 (both 2 × ArCH), 134.7 (ArCH) and 139.5 (ArC); *m/z* [ES] 342 (M^+ + H, 100%) [Found: M^+ + H, 342.1375. $C_{16}H_{23}NO_5S$ requires *M*, 342.1375]. Selected NOE data: 2-H/5-H (5.9%); 2-H/N-Me (2.6%); 5-H/N-Me (2.3%); 5- Me/N-Me (< 1%); N-Me/CH_2SO_2 (< 1%).

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