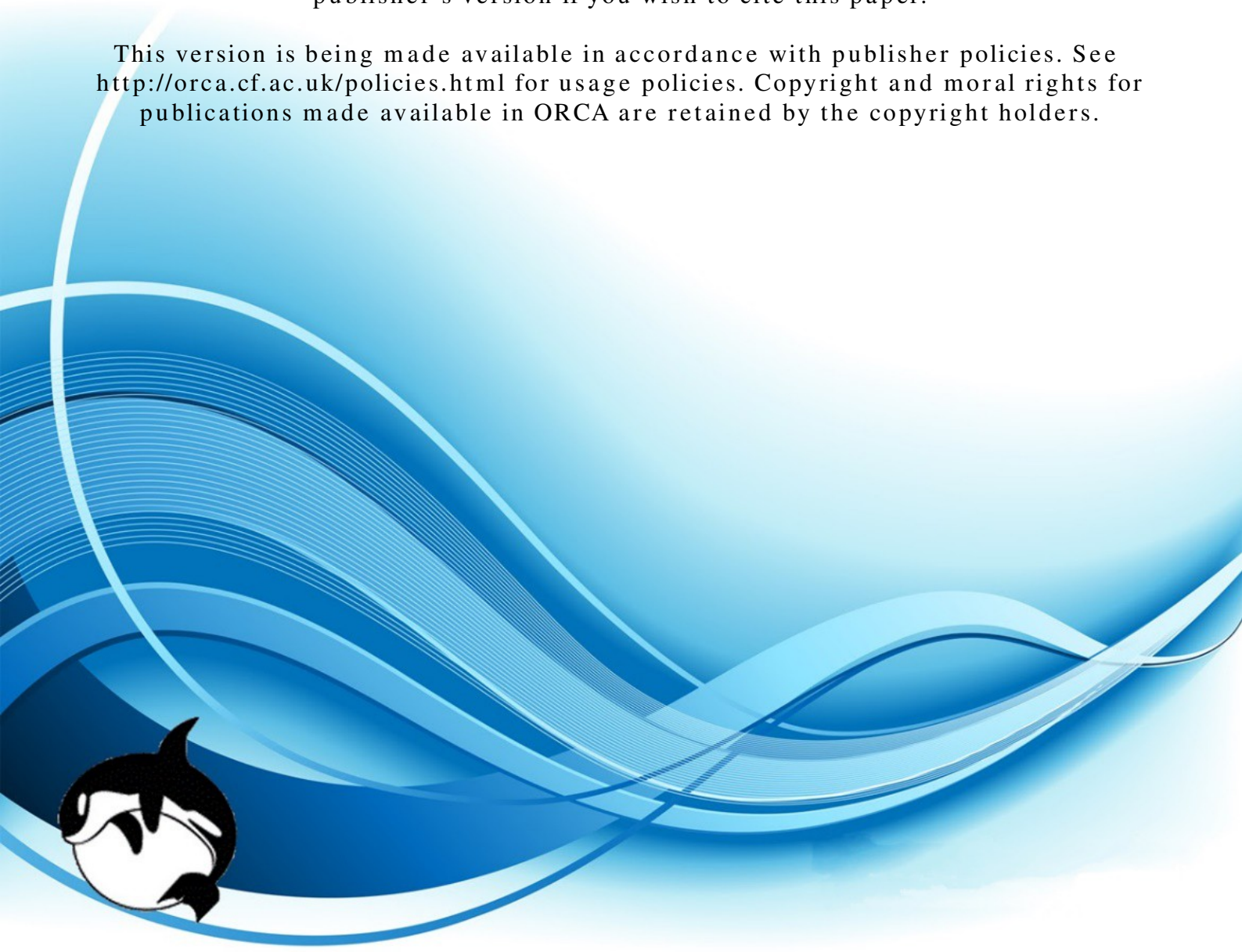

Tetrahedron Letters

# A new method for the synthesis of pyrazolidines

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abstract

Fully protected pyrazolidines can be readily obtained by acid-catalysed cyclisations of the corresponding allylic hydrazines by carbenium ion generation using concentrated sulfuric acid in dichloromethane.

Pyrazoles and their partly and fully reduced derivatives, pyrazo-lines and pyrazolidines, form an important group of heterocycles, with potentially important contributions to make to drug design by reason of their ability to form strong hydrogen bonds at either or both nitrogen atoms. It is perhaps also signiÞcant that Nature does not seem able to form NAN bonds directly and hence such compounds will occupy an entirely non-natural portion of chemi-cal space and hence are likely to continue to play a central role in the discovery of novel pharmaceuticals.[1] Despite the enormous contribution made by heteroaromatic residues, both with and without incorporated nitrogen atoms in a majority of commercial drug structures, it has recently become plain that to achieve a con-tinuation of this success, it would be wise to embrace semi-satu-rated and fully saturated analogues of such structural features, in order to introduce both greater ßexibility and increased three dimensional shape.[1]

Many synthetic routes have been deÞned for the syntheses of such heterocyclic systems, but quite often these suffer from a lack of regioselectivity, particularly when both CAN bonds are formed effectively simultaneously from a hydrazine and an all-carbon bis-electrophile such as a 1,3-dicarbonyl or a conjugated enone.[2] Hence, often it is preferable to assemble such structures using a stepwise approach.[3,4] The inspiration for the present methodology was derived from a possible extension of our Þnding that unsatu-rated sulfonamides 1 are readily converted into the corresponding pyrrolidines 2 following exposure to acid,[5] in an intramolecular hydroamination reaction. A particularly rapid and efÞcient exam-ple (Scheme 1) features favourable tertiary carbenium ion genera-tion by protonation of the alkene group in the precursor sulfonamide 1, which is then trapped by the sulfonamide group to give an essentially quantitative yield of the corresponding pyrrolidines 2.

Such cyclisations are quite general and are also successful when secondary carbenium generation is required. The fact that concen-trated sulfuric acid can be used in less than stoichiometric quanti-ties gives the method some positive environmental credentials as the only by-product of these usually very clean cyclisations is the sodium or potassium sulfate generated upon mild, basic work-up. Of course, the highly acidic nature of the method will impose some restrictions on future applications; thus far, remote alkenes, alkynes, sulfones, esters and alcohols protected as the correspond-ing acetates have been found to be stable and not to interfere with such cyclisations. It was against this background that we wondered if such methodology could be extended to include cyclisations of suitably protected allylic hydrazines 3 which, if successful, would result in the deÞnition of a new and perhaps efÞcient approach to pyrazolidines 4 (Scheme 2).

Herein, we report our preliminary results, which show that this idea is indeed viable. A recent report strongly suggested that the methodology shown in Scheme 2 would be successful. In this study, the discovery of novel, two-step cyclisations was described in which the acylhydrazones 5 having a distal prenyl alkene under-went conversion into the annulated pyrazolidines 7 (Scheme 3).[4] A likely mechanism involves imine protonation followed by cyclisa-tion to form a cyclohexane which generates exactly the type of

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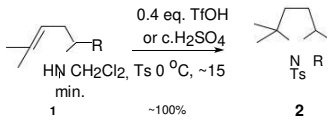
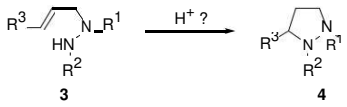
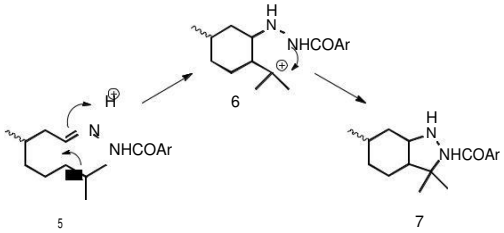


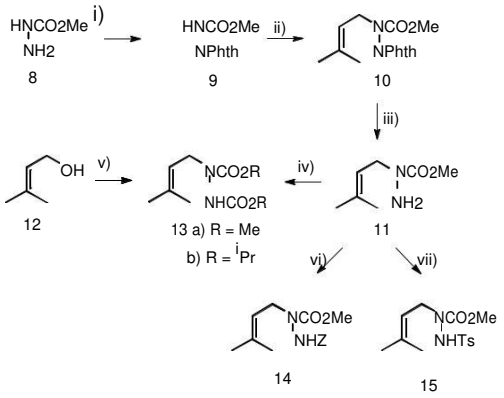

Scheme 1. Intramolecular, acid-catalysed hydroamination.




Scheme 2. Idea: would protected hydrazines cyclise?




Scheme 3. Acid-catalysed imine cyclisation: possible mechanism.[4]

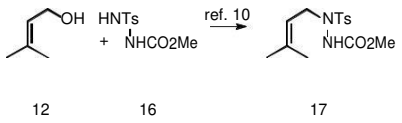



Scheme 4. Starting material synthesis: Reagents and conditions: (i) (a) phthalic anhydride, THF, rt, 0.5 h; (b) DCC, rt, 18 h, add HOAc and $Et_3N$, reßux, 1 h (95%); (ii) $Ph_3P$, THF, 0 LC, DIAD, 0 LC, 0.25 h, alcohol 12, 0 LC, 0.25 h, add hydrazine 9, then rt, 18 h (87%); (iii) $MeNHNH_2$, $CH_2Cl_2$, EtOH, 0 LCÐrt, 18 h (96%); (iv) $K_2CO_3$, $Et_2O$, $H_2O$, amine 11, add $ClCO_2Me$, rt, 2 h (92%); (v) diisopropyl azodicarboxylate, $Ph_3P$, $Et_2O$, rt, 18 h (ca. 50%); (vi) as (iv) with $ClCO_2Bn$ (97%); (vii) TsCl, pyridine, $CH_2Cl_2$, 0Ð 20 LC, 18 h (92%).

tertiary carbenium ion 6 featured in our pyrrolidine synthesis (Scheme 1), subsequent trapping of which by the newly generated hydrazine leads to the observed products 7. Of course, as pointed out,[4] alternative mechanisms could well be in operation, but at least a compatibility between such masked hydrazines and an acid-catalysed reaction looked likely.[5]

We relied on the Mitsunobu reaction[6] to obtain suitable sub-strates for our investigation of the idea shown in Scheme 2, as out-lined in Scheme 4.

Starting with methyl carbazate 8, addition to phthalic anhy-dride followed by carbodiimide-induced cyclisation gave the dou-bly protected hydrazine 9.[7] A Mitsunobu coupling of this intermediate with prenyl alcohol 12 then gave fully substituted hydrazine 10, the Ing-Manske deprotection of which led to the free amine 11. Coupling of this with a chloroformate or tosyl chloride then gave precursors 13a, 14 and 15 in generally excellent yields. More directly, prenyl alcohol 12 was converted into the




Scheme 5. Regioselective Mitsunobu coupling.

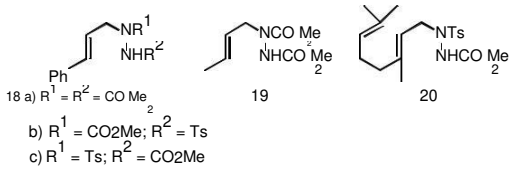



Figure 1. Hydrazines from cinnamyl, crotyl and geranyl alcohols.

symmetrically protected hydrazine 13 by a Ôhalf-MitsunobuÕ wherein no additional nucleophile is added; the hydrazine by-pro-duct plays this role.[8] Although more rapid, this direct method never gave much above a 50% yield after careful chromatography and hence the lengthier route was preferred. It did however pro-vide useful structural conÞrmation of the assigned structures 13 and others. The isomer 17 of the mixed carbamateÐsulfonamide protected hydrazine 15 was prepared by a direct, regioselective Mitsunobu alkylation of alcohol 12 (Scheme 5).[9]

The methods shown in Scheme 4 were also used to prepare rep-resentative phenyl- 18aÐc and a methyl-substituted hydrazine 19 along with the geranyl derivative 20 using cinnamyl, crotyl and geranyl alcohols respectively, in similarly good yields (Fig. 1).

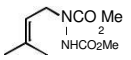
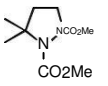
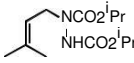
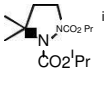
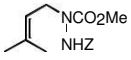
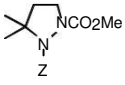
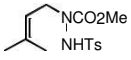
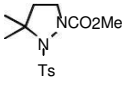
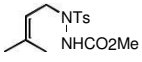
In general, the precursors 13Ð15 and 17Ð20 were readily puri-Þed by column chromatography and subsequently characterised by the usual criteria. However, line broadening was usually evident in both $^1H$ and $^{13}C$ NMR spectra, due to restricted rotation. For example, at 400 MHz in $CDCl_3$, the symmetrically protected preny-lated hydrazine 13a showed a pair of broad resonances for the NH group ($\delta_H$ 6.6 and 6.8) in a ratio of ca. 2:1 but, when combined, integrating accurately for one proton, together with an indistinct methylene resonance centred at $\delta_H$ 4.04 and one sharp and one slightly broadened methoxy resonances at $\delta_H$ 3.65 and 3.63. Simi-larly, in the $^{13}C$ NMR spectrum, whilst the two allylic methyl groups and one of the methoxy groups appeared as very sharp res-

onances, the alkene methine (:CH) was slightly broadened and all remaining resonances were very broad. In practice, once such fea-tures became familiar, these served as highly characteristic pat-terns enabling identiÞcation of such products.

Our initial attempts to carry out the cyclisation summarised in Scheme 2 were focussed on the precursor 13a as it should be amongst the easiest to convert into a tertiary carbenium ion and also contained robust, acid-resistant protecting groups. Catalysis of the desired cyclisation using two contrasting acids, concentrated sulfuric and trißuoromethanesulfonic (trißic) acid, was examined.[5] Sulfuric acid is poorly soluble in dichloromethane, the most suit-able solvent for such chemistry so far identiÞed,[10] and hence may react in a quite different manner with freely soluble trißic acid.[11]

We were pleased to Þnd that stirring the methoxycarbonyl-pro-tected hydrazine 13a with 0.5 equiv of concentrated sulfuric acid in dichloromethane[11] at ambient temperature overnight resulted in complete disappearance of the staring material and isolation of a single product 21 in excellent yield. Similar excellent yields were also obtained but more rapidly by gently reßuxing the reac-tion mixture for three hours or using trißic acid, when the cyclisa-tion occurred at ice temperature in around two hours. In all cases, work-up was simple: the acid was neutralised using saturated aqueous potassium carbonate and the separated organic layer washed with water then dried ($MgSO_4$) and evaporated.

Table 1
Acid-catalysed cyclisations of hydrazines 13Ð15 and 17

| Precursor | Conditions | Product | Yield |
|---|---|---|---|
|  **13a** | 0.5 eq c.$H_2SO_4$<br>20 LC, $CH_2Cl_2$ 18 h<br>0.5 eq c.$H_2SO_4$<br>40 LC, $CH_2Cl_2$ 3 h<br>0.5 eq TfOH<br>0 LC, $CH_2Cl_2$ 2 h |  **21** | 95%<br>93%<br>97% |
|  **13b** | 0.5 eq c.$H_2SO_4$<br>20 LC, $CH_2Cl_2$ 22 h<br>0.5 eq c.$H_2SO_4$<br>40 LC, $CH_2Cl_2$ 3 h |  **22** | 94%93% |
|  **14** | 0.5 eq c.$H_2SO_4$<br>40 LC, $CH_2Cl_2$ 3 h |  **23** | 96% |
|  **15** | 0.5 eq c.$H_2SO_4$<br>0 LC, $CH_2Cl_2$ 1 h |  **24** | 98% |
|  **17** | 0.5 eq c.$H_2SO_4$<br>0 LC, $CH_2Cl_2$ <1 h |  **25** | 94% |

Under more vigorous conditions than these, or if the trißic acid was wet, variable loss of the protecting groups was evident from NMR spectra of the crude products. The pattern was much the same with cyclisations of the related bis-isopropyloxycarbonyl derivative 13b, which was converted into the pyrazolidine 22 under similar conditions. Somewhat to our surprise, the benzy-loxycarbonyl (Z) group also survived heating to 40 LC to give an equally good yield of the pyrazolidine 23 (Table 1). Exchanging one of the carbamate groups for a sulfonamide function acceler-ated the cyclisations, both examples of which (15 ? 24 and 17 ? 25) proceeded rapidly at 0 LC. In the case of substrate 15, a lower $pK_a$ of the NAH bond to be broken may be responsible,[9] whilst in the latter example, perhaps greater steric compression due to the tosyl group assists the conversion to pyrazolidine 25. Overall, the reaction conditions are commensurate with the inter-mediacy of a tertiary carbenium ion and are relatively close to our previous observations.[5]

Structural proof of the products was straightforward, although there were a few unexpected characteristics. Disappearance of

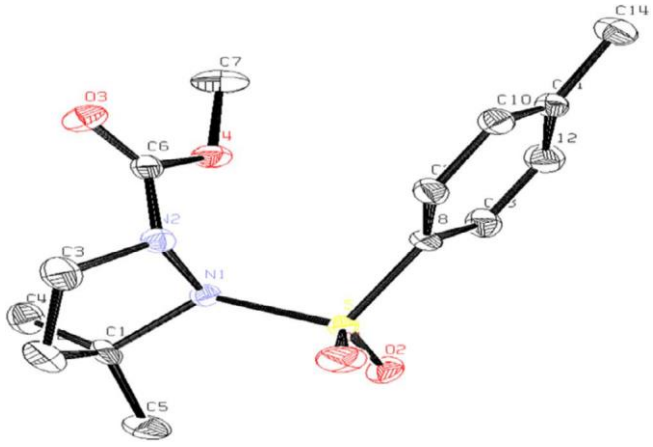



Figure 2. ORTEP diagram of product 24.

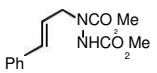
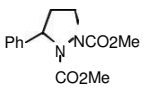
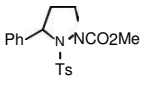
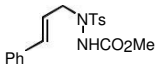
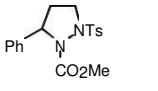
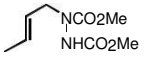
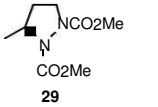
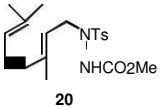
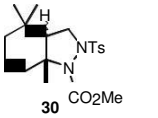
the resonance for the alkene methine around $d_H$ 5.2 was the clear-est sign of complete reaction. The products all showed similar degrees of resonance broadening due to restricted and/or pseudo-rotation. For example, in the $^1H$ NMR spectrum of the pyra-zolidine 13a, in $CDCl_3$ at 400 MHz and 32 LC, the two methoxy groups occurred as sharp singlets at $d_H$ 3.65 and 3.67, whilst the geminal methyl groups appeared as a sharp single resonance at $d_H$ 1.41. However, the methylene group remote from nitrogen appeared as a diffuse, broad signal centred on $d_H$ 1.88 and the two protons of the methylene group adjacent to nitrogen as two diffuse signals centred at $d_H$ 3.93 and $d_H$ 3.18. On warming to 50 LC, the N-$CH_2$ resonances became very broad but the signal due to the other methylene group resolved into a triplet ($d_H$ 1.87, J = 6.7 Hz). By contrast, when the same sample was used to obtain a $^{13}C$ proton-decoupled spectrum under the same conditions, all resonances were sharp except for the geminal methyl groups, which appeared as very broadened resonances centred on $d_C$ 25.3 and 27.4 ppm. Similar effects were observed throughout this ser-ies; in many cases, heating the sample in $d_6$-DMSO produced an even less informative $^1H$ NMR spectrum.

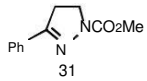
In a similar fashion, the mixed carbamateÐsulfonamide 24 showed sharp resonances for the tosyl and methoxy groups in its $^1H$ NMR spectrum in $CDCl_3$ at 32 LC, but separate, broadened reso-nances for each of the ring protons, centred on $d_H$ 3.64, 3.43, 1.94 and 1.75 and two broadened singlets for the geminal methyls cen-tred at $d_H$ 1.61 and 0.97. Once again, all resonances in the $^{13}C$ spec-trum were sharp, except for the methyls which, as in previous examples, appeared as very broadened resonances centred on 24.2 and 28.3 ppm. To be certain of these structural assignments, we carried out an X-ray crystallographic analysis of product 24, the result of which is shown in Figure 2.[12]

We then continued onto a study of related cyclisations of the less highly substituted substrates 18aÐc and 19, each of which would give a less stabilised carbenium ion when protonated at the alkene function (Table 2).

In the event, the cyclisations proceeded well under conditions which correlated well with the stability of the intermediate carbe-nium ion. Using either concentrated sulfuric or trißic acid, cyclisa-tions of the representative cinnamyl derivatives 18aÐc either

Table 2
Acid-catalysed cyclisations of hydrazines 18aÐc, 19 and 20

| Precursor | Conditions | Product | Yield |
|---|---|---|---|
|  **18a** | 0.5 eq c.$H_2SO_4$<br>40 LC, $CH_2Cl_2$ 6 h<br>0.5 eq TfOH<br>35 LC, $CH_2Cl_2$ 4 h |  **26** | 93%<br>96% |
|  **18b** | 0.5 eq c.$H_2SO_4$<br>20 LC, $CH_2Cl_2$ 44 h<br>0.5 eq c.$H_2SO_4$<br>40 LC, $CH_2Cl_2$ 3 h |  **27** | 87%<br>79% |
|  **18c** | 0.5 eq c.$H_2SO_4$<br>20 LC, $CH_2Cl_2$ 40 h |  **28** | 95% |
|  **19** | 0.5 eq c.$H_2SO_4$<br>85 LC, $CH_2Cl_2$ 22 h |  **29** | 90% |
|  **20** | 0.5 eq c.$H_2SO_4$<br>0 LC, $CH_2Cl_2$ 1 h |  **30** | 98%<br>[3:2 t/c] |




31

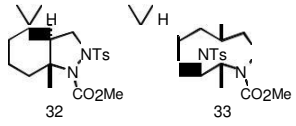
Figure 3. Elimination product from 18b.

required heating for 3Ð6 h in dichloromethane or a more pro-longed reaction time at ambient temperature. At least with these substrates, yields were again excellent.

Lengthier reaction times again began to cause loss of the pro-tecting groups. In the case of the NHTs derivative 18b, 18 h expo-sure to c.$H_2SO_4$ at ambient temperature led to clean conversion but only to an extent of ca. 50%. In contrast, under both conditions mentioned in Table 2, formation of an isolable by-product was evi-dent (5 10%), which turned out to be compound 31, formed by elimination of toluenesulÞnic acid. This showed characteristic apparent triplets at $d_H$ 3.94 and 3.19, along with other consistent features. Similar elimination products were thought to be present in the crude reaction mixtures isolated from reactions of the other two cinnamyl-based precursors but were not isolated and there-fore not identiÞed with certainty (Fig. 3).

Predictably, the corresponding crotyl derivative 19 required the much more vigorous conditions of reßux in dichloroethane in order to induce cyclisation. Nevertheless, a decent yield of the hoped-for pyrazolidine 29 was isolated, but once again there was evidence for the loss of protecting groups although no products from this were isolated. The products 26Ð29, in contrast to the foregoing gem-dimethyl derivatives (Table 1), exhibited largely Þrst order NMR spectra, with only minimal line broadening.

A Þnal example featured an attempt to use a cascade cyclisation to form a bicyclic derivative. As this would be a return to the inter-mediacy of tertiary carbenium ions, it was expected to proceed under much milder conditions. In the event, the geranyl-substi-tuted hydrazine 20 was smoothly converted into a mixture 30 of two separable products, in a ratio of ca. 3:2, at 0 LC in under one hour. These were assigned as the trans- and cis-fused products 32 and 33 (Fig. 4), on the basis of some rather poor quality NOE evidence.




32 33

Figure 4. trans- and cis-isomers of product 30.

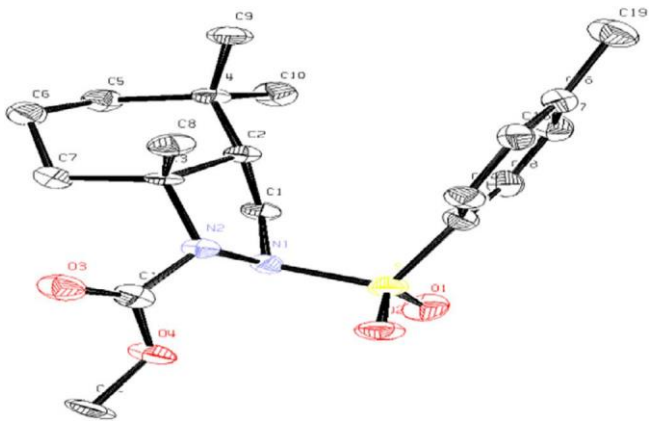



Figure 5. ORTEP diagram of the cis-isomer 33.

Fortunately, both were crystalline solids and so X-ray crystallo-graphic analysis was used to conÞrm these assignments, by mea-
surement of the minor isomer 33, the resulting ORTEP diagram of which is shown in Figure 5.[13]

Some resonances were characteristic of the two isomers in their $^1$H NMR spectra: in the trans-isomer 32, one of the protons a-to nitrogen appeared as a dd pattern (J = 13.2 and 11.0 Hz) at $d_H$ 3.22 and a relatively sharp methoxy signal resonating at $d_H$ 3.63 whereas in the cis-isomer 33, the corresponding protons resonated as an apparent triplet (J = 13.0 Hz) at $d_H$ 3.09 and a very broadened resonance centred on $d_H$ 3.40.

These model studies have therefore established that the cyclisa-tions shown in Scheme 2 are indeed viable, despite the presence of two albeit protected nitrogen atoms. Given due attention to the stability or otherwise of additional substituents, this combination of Mitsunobu coupling or, in the future, other CAN formation methods and the acid-catalysed cyclisation should provide viable and regiospeciÞc access to many types of pyrazolidines.

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## References and notes

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10. When temperatures above 45 LC were required, dichloroethane, bp. 84 LC, was used. As concentrated sulfuric acid can only be largely suspended in dichloromethane, measuring ÔstandardizedÕ mixtures was also quite inaccurate.

11. Typically, 0.5 equiv of acid was used with respect to the precursor hydrazine. Reactions were carried out in anhydrous dichloromethane under dry nitrogen. Trißic acid was measured by syringe and added to the solution. Concentrated sulfuric acid was measured dropwise by glass pipette; typically 30 mg (two drops) was added to 4 mL of dry dichloromethane.

12. X-ray analysis of pyrazolidine 24: $C_{14}H_{20}N_2O_4S$, Mr = 312.38, Triclinic, P1, a = 8.2711(4) •, b = 9.5914(6) •, c = 10.2058(6) •, a = 106.254(3)L, b = 95.929 (3)L, c = 95.034(3)L, V = 767.33(8) •$^3$, Z = 2, Dx = 1.352 Mg m$^{-3}$, k(Mo Ka) = 0.71073 •, l = 0.228 cm$^{-1}$, F(0 0 0) = 332, T = 160(2) K, crystal size = 0.30 0.30 0.12 mm$^3$, Reßections collected = 5124, Independent reßections = 3689, 2555 with $F_o > 4$ s ($F_o$), $R_{int}$ = 0.0462, Final R1 = 0.0892, wR2 = 0.1832 for I > 2sigma(I), and R1 = 0.1267, wR2 = 0.199 for all data. The CIF Þles have been deposit at Cambridge Crystallographic Deposit Center with registry number CCDC 888756.

In the crystal, the toluene and methyl ester groups adopt a cis conformation. The other face of the phenyl ring overlaps partly with a ring from a neighbouring molecule resulting in intermolecular pÐp interaction.

13. X-ray analysis of pyrazolidine 33: $C_{19}H_{28}N_2O_4S$, Mr = 380.49, Triclinic, P1, a = 8.8933(6) •, b = 10.0576(6) •, c = 11.9571(5) •, a = 73.913(3)L, b = 73.257 (3)L, c = 80.234(3)L, V = 979.36(10) •$^3$, Z = 2, Dx = 1.290 Mg m$^{-3}$, k(Mo Ka) = 0.71073 •, l = 0.191 cm$^{-1}$, F(0 0 0) = 408, T = 160(2) K, crystal size = 0.35 0.25 0.09 mm$^3$, Reßections collected = 6520, Independent reßections = 4575, 2410 with $F_o > 4$ s ($F_o$), $R_{int}$ = 0.0598, Final R1 = 0.0914, wR2 = 0.1806 for I > 2sigma(I), and R1 = 0.1887, wR2 = 0.2244 for all data. The CIF Þles have been deposit at Cambridge Crystallographic Deposit Center with registry number CCDC 888757.

The toluenesulfonyl and methyl ester groups adopt a trans conformation in the crystal. The phenyl ring is involved in pÐp interactions through partial overlap with a ring from a neighbouring molecule. The closest contact made by the opposite face of the ring is through the tertiary hydrogen, with an intramolecular CÐH ring-centroid interaction of ca. 2.7 •.