Tetrahedron: Asymmetry Vol. 2, No. 10, pp. 997-1000, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Development of Chiral Stabilised Azomethine Ylids: Completing the Memory Relay¶

Amberley S. Anslow,[a] Laurence M. Harwood,[a]* Helen Phillips[a] and David Watkin[b]

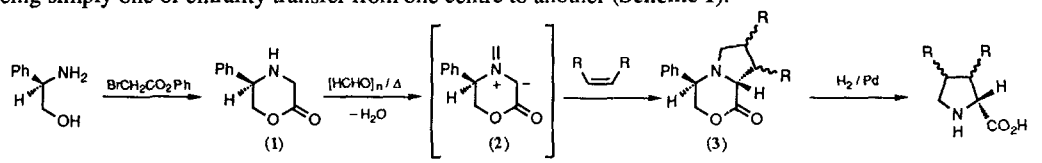
[a] *Dyson Perrins Laboratory, University of Oxford, South Parks Road, OXFORD OX1 3QY.*

[b] *Chemical Crystallography Laboratory, University of Oxford, Parks Road, OXFORD OX1 3PD.*

(*Received* 2 *September* 1991)

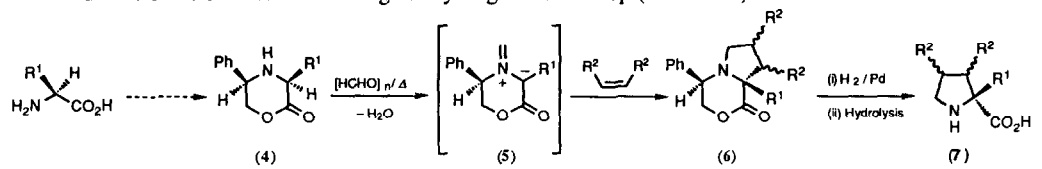
Abstract: We report how the α–chirality of *L*–valine can be "memorised" through a sequence involving chirality transfer to a cyclic template, followed by azomethine ylid generation and enantiospecific cycloaddition to regenerate the centre lost during ylid formation. Subsequent removal of the chiral template furnishes α–substituted *D*–proline derivatives.

We have recently described[1a] how (5*R*)–phenylmorpholin–2–one (**1**)[2] prepared from (*R*)–phenylglycinol may be used to generate the chiral stabilised azomethine ylid (**2**) which undergoes enantioselective 1,3–dipolar cycloadditions with a range of dipolarophiles giving cycloadducts (**3**) with total enantiocontrol by the chiral centre at C–5 over the new chiral centre generated at C–3. In such a sequence 5–phenylmorpholin–2–ones can act as "chiral glycine" equivalents for azomethine ylid generation, permitting access to homochiral proline derivatives after hydrogenolysis of the cycloadducts.[3] However, this deprotection step results in destruction of the chirality at C–5 of the morpholin–2–one template with the overall sequence being simply one of chirality transfer from one centre to another (**Scheme 1**).



Scheme 1

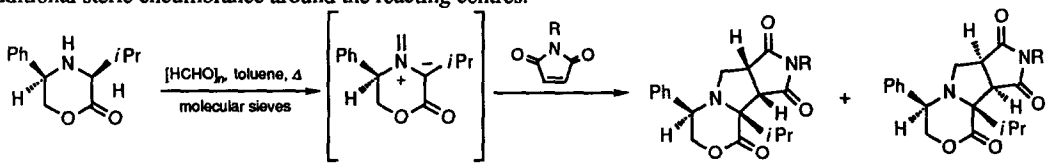
Sacrifice of the chiral template would be more justifiable if the C–5 chirality could be generated during construction of a 3,5–disubstituted morpholin–2–one (**4**) by combination of a prochiral precursor with an α–amino acid; thus providing a transient "chiral memory" of the α–amino acid to counter the fact that the chiral information at the original centre is necessarily lost during generation of the ylid (**5**). In such a sequence, hydrogenolysis and hydrolysis of the resultant cycloadducts (**6**) is predicted to furnish unnaturally configured, α–substituted proline derivatives (**7**) in which information regarding the absolute stereochemistry of the α–amino acid centre has been carried through the ylid generation step (**Scheme 2**).



Scheme 2

¶ Dedicated to the memory of Tom V. Lee, deceased 26 June 1991.

In this Communication we report the realisation of such a chiral relay system commencing with *L*–valine and profiting from the work of Caplar who has demonstrated that hydrogenation of the cyclic condensation product derived from *L*–valine and α–bromoacetophenone occurs stereospecifically to furnish homochiral **8**.[4] Subsequent reaction of **8** with paraformaldehyde in refluxing toluene, following a modified method based on that of Tsuge *et al*,[5] yielded the homochiral azomethine ylid (**9**) as evidenced by trapping *in situ* with *N*–phenyl maleimide, to furnish the *endo*– adduct (**10a**) {34%, $[\alpha]_D^{20} = -42.8$ (c = 1.30, $CHCl_3$)} and the *exo*– adduct (**11a**) {7%, $[\alpha]_D^{20} = -1.08$ (c = 1.0, $CHCl_3$)}.[6] Reaction of **8** with paraformaldehyde in the presence of *N*–methyl maleimide gave the *endo*– adduct (**10b**) {46%, $[\alpha]_D^{20} = +51.9$ (c = 0.78, $CHCl_3$)} as the only identifiable material (**Scheme 3**). Morpholin–2–one (**8**) appears to be stable indefinitely at room temperature unlike the unsubstituted parent (**1**) and this additional stability appears to be reflected in the need for higher reaction temperatures with marginally lowered material yields and improved *endo*– : *exo*–adduct ratios observed, compared with cycloadditions utilising **1**.[1a] These observations may be rationalised as being the consequence of additional steric encumbrance around the reacting centres.



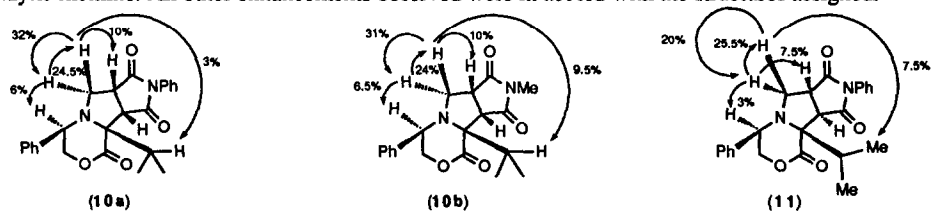
(8) (9) (10) (11)

a R = Ph 34% 7%

b R = Me 46% –

Scheme 3

NOE difference experiments permitted assignment of the *endo*– and *exo*– stereochemistries of the adducts and the important diagnostic data are shown in **Figure 1**. In the cases of the *endo*– adducts (**10a, b**), irradiation of the β–hydrogen of the methylene group adjacent to the nitrogen caused the expected large enhancement of its geminal partner. However, enhancements of the adjacent methine proton and the methine of the isopropyl group were also observed, indicating their mutual β–disposition. Irradiation of the second proton of this methylene group caused an enhancement of the benzylic methine of the morpholin–2–one ring, confirming the α–stereochemistry of both protons, in addition to a major enhancement of its geminal partner. In the *exo*–adduct (**11**), irradiation of the β–hydrogen of the methylene group adjacent to the nitrogen resulted in enhancement of its geminal partner and of the diastereotopic methyl group occurring at higher field. Conversely, irradiation of the α–proton led to enhancement of the adjacent methine proton as well as its geminal partner and the benzylic methine. All other enhancements observed were in accord with the structures assigned.

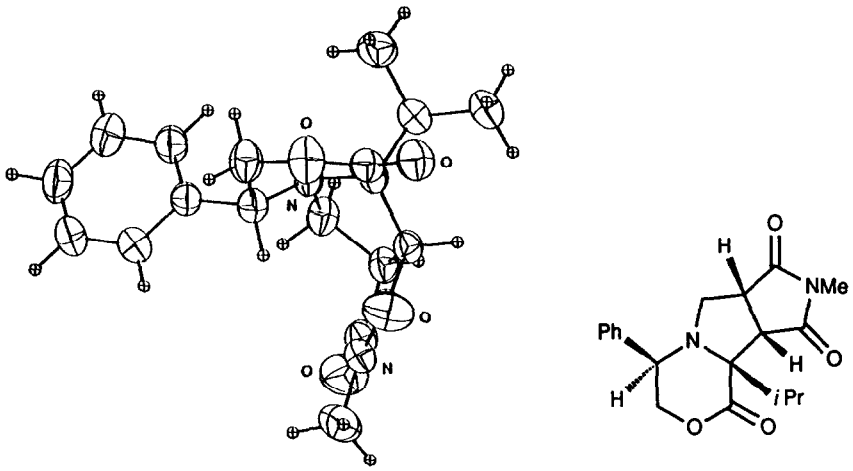


(10a) (10b) (11)

Figure 1

Confirmation for these assignments came from X–ray crystallographic analysis of the *endo*– isomer (**10b**) which showed the morpholin–2–one ring to exist in a flattened conformation in which both heteroatoms,

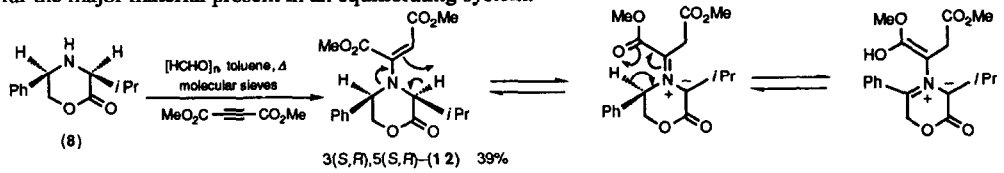
the carbonyl carbon and the quaternary carbon are almost coplanar. It also clearly demonstrated how the *endo*–configuration minimises steric interactions between the isopropyl group and the imide ring (**Figure 2**).[7]



X–ray crystal structure of *endo*– adduct (**10b**)

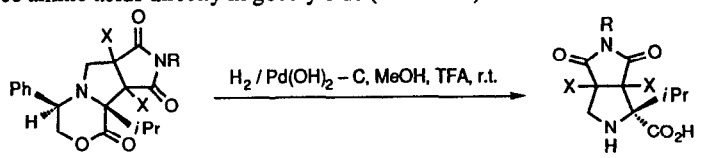
Figure 2

No adduct was observed when **8** was heated with paraformaldehyde in the presence of dimethyl maleate as the potential dipolarophile, and use of dimethyl acetylenedicarboxylate resulted in a diversion of the desired reaction, leading instead to formation of the Michael adduct (**12**) in 39% isolated yield after chromatography. This adduct was found to show no optical rotation at a series of wavelengths. We rationalise this result by invoking racemisation under the conditions of thermolysis *via* a sequence such as that shown in **Scheme 4** involving a series of prototropic shifts. We were not able to detect the presence of the other diastereomers which might be expected to be formed in this process, but 3,5–*syn*–disubstituted adduct (**12**) would be expected to be by far the major material present in an equilibrating system.



Scheme 4

It was found that benzylic hydrogenolysis of adducts **10a,b** and **11a** using Pearlman's catalyst[8] in methanol, containing a few drops of trifluoroacetic acid, occurred smoothly with concommittant hydrolysis of the ester to yield the free amino acids directly in good yields (**Scheme 5**).



10a X = β–H, R = Ph
10b X = β–H, R = Me
11 X = α–H, R = Ph

13 72%
14 77%
15 74%

Scheme 5

Endo– adduct (**10a**) formed proline derivative (**13**) {72%, $[\alpha]_D^{20}$ = –21.3 (c = 0.78, 1M HCl)}, *endo*-adduct (**10b**) yielded **14** {77%, $[\alpha]_D^{20}$ = +15.3 (c = 0.75, 1M HCl) and *exo*– adduct (**11**) furnished **15** {74%, $[\alpha]_D^{20}$ = +19.6 (c = 0.75, 1M HCl)}. As the hydrogenolysis products **13** – **15** were obtained from chiral precursors which had been shown to be diastereomerically pure to the limits of spectroscopic detection, and as we have previously shown that there is no loss of integrity of the chiral centre at C–5 during ylid generation and subsequent trapping,[1a] it may be concluded that **13** – **15** are essentially homochiral. Thus far, attempts at corroborating the enantiomeric integrity of these proline derivatives by ^{19}F NMR analysis of the Mosher's amide derivatives[9] derived from the corresponding methyl esters of **13** – **15** (CH_2N_2, MeOH, r.t.) have been thwarted by difficulties in preparing the sterically hindered amides.

In conclusion, we have demonstrated that the 5–phenylmorpholin–2–one (**8**) derived from *L*–valine may be used as a transient template to transmit chirality information through formation and trapping of an azomethine ylid (**9**), acting as a "chiral memory" for the α–amino acid centre which must lose its chirality during ylid generation. In addition to this chiral relay at the α–position, the strong *endo*– preference of the [3 + 2] cycloaddition results in the enantiocontrolled construction of two new chiral centres on the pyrrolidine ring. Subsequent dismantling of the morpholin–2–one template by concommitant hydrogenolysis and hydrolysis in one pot furnishes α–substituted *D*–proline derivatives efficiently. We will report our further studies and applications of this protocol in due course.

Acknowledgement We gratefully acknowledge support for this work from the S.E.R.C. (A.S.A), and valuable assistance from Mrs Elizabeth McGuiness in carrying out NMR analyses.

References

1. (a) A.S.Anslow, L.M.Harwood, H.Phillips and D.Watkin, *Tetrahedron Asymmetry*, 1991, **3**, 169. For other systems involving enantioselective 1,3–dipolar additions to azomethine ylids see: (b) A. G. H. Wee, *J. Chem. Soc. Perkin Trans. 1*, 1989, 1363; (c) J.Rouden, J. Royer and H–P. Husson, *Tetrahedron Lett.*, 1989, 5133; (d) S. Kanemasa and H. Yamamoto, *Tetrahedron Lett.*, 1990, 3633; (e) D. A. Barr, M. J Dorrity, R. Grigg and J. F. Malone, *Tetrahedron Lett.*, 1990, 6569.
2. J.F. Dellaria, Jr. and B.D. Santarsiero, *J. Org. Chem.*, 1989, **54**, 3916. In this paper we use the trivial morpholin–2–one nomenclature to describe the 2,3,5,6–tetrahydro–*4H*–oxazinone ring system.
3. Morpholin–2–one substrates have been previously utilised as chiral glycine templates *via* cationic and anionic protocols. See: (a) R. M. Williams and J. A. Hendrix, *J. Org. Chem.*, 1990, **55**, 3723; R. M. Williams and M–N. Im, *Tetrahedron Lett.*, 1988, 6075, and references cited therein and (b) D. S. Reno, B. T. Lotz and M. J. Miller, *Tetrahedron Lett.*, 1990, 827.
4. V. Caplar, A. Lisini, F. Kajfez, D. Kalbah and V. Sunjic, *J.Org.Chem.* , 1978, **43**, 1355.
5. O. Tsuge, S. Kanemasa, M. Ohe and S. Takenaka, *Chem. Lett.*, 1986, 973.
6. All novel compounds isolated gave spectroscopic and combustion analytical data in accord with their assigned structures.
7. *Crystal data* for (**10b**): $C_{19}H_{22}N_2O_4$, monoclinic, $P2_1$, a =9.803, b = 7.758, c = 11.518 Å, α = 89.97, β = 90.30, γ = 90.01°, V = 875.9 Å^3, Z = 2, D_c = 1.298 g cm^{-3}, $F(000)$ = 364, μ(Cu–K_α) = 7.117 cm^{-1}. 1938 Independent reflections with $I > \sigma(I)$ were used in the analysis. Final R = 3.54, final Hamiltonian weighted R = 4.33. Data for crystallographic analysis were measured ($2\theta_{max}$ = 150°) on an Enraf–Nonius CAD 4 diffractometer using Cu–K_α radiation and ω–2θ scans. Structures were solved by direct methods and refined by least squares using the CRYSTAL package. Atomic co–ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
8. P. N. Rylander, *Catalytic Hydrogenation in Organic Syntheses"*, Academic Press, N.Y., 1979, p. 280.
9. T. Kusumi, T. Fukushima. I. Ohtani and H. Kakisawa, *Tetrahedron Lett*, 1991, 2939, and references cited therein.