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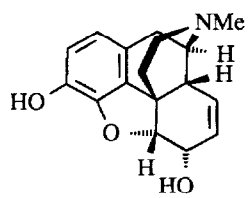
A CONCISE APPROACH TO THE MORPHINAN SKELETON USING A TANDEM INTRAMOLECULAR FURAN DIELS-ALDER / RADICAL CYCLISATION STRATEGY

Harry Finch,*[a] Laurence M. Harwood,*[b] Graeme M. Robertson,[a] and Richard C. Sewell.[b]

a Glaxo Group Research Ltd, Park Road, WARE, SG12 0DJ.
b Dyson Perrins Laboratory, University of Oxford, South Parks Road, OXFORD OX1 3QY.

A sequence involving an intramolecular Diels-Alder reaction of a furan diene possessing an allenic amide dienophilic moiety, followed by radical induced annelation of the resultant cycloadduct, permits access to material possessing a functionalised morphinan skeleton.

In an extension of our studies into synthetic applications of the intramolecular Diels - Alder reaction of furans (IMDAF),[1] we have become interested in the subsequent annelation of the initial cycloadducts to furnish more complex multicyclic frameworks, such as that found in morphine (**1**)[2]



(**1**)

It was envisaged that an efficient approach to morphinan type structures would involve initial IMDAF using an allenic amide as the dienophilic moiety to construct the heterocyclic ring, followed by either anion or radical mediated 1,4- addition to the α,β- unsaturated amide moiety formed in the resultant cycloadduct (**Figure 1**).

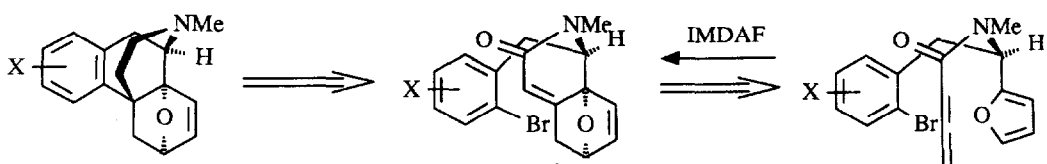
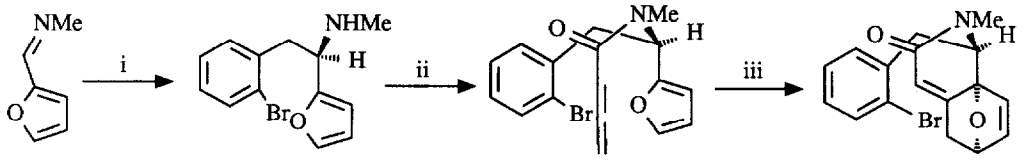


Figure 1

In our choice of this approach we were greatly influenced by the elegant work of Kanematsu[3] which has demonstrated the ready propensity of allenic dienophiles to undergo IMDAF at the terminal double bond. During the course of this work Hart[4] communicated work based upon a similar protocol using an

*inter*molecular cycloaddition / radical cyclization sequence. In our system however, we were aware of additional potential difficulties, both in stereochemical control of the IMDAF, and in the subsequent annelation which requires construction of a quaternary centre.[5]

To investigate the potential of such an approach, the benzylic Grignard reagent derived from 2-bromobenzyl bromide was added to *N*-methyl 2-furylimine[6] and the resulting amine (**2**) acylated with prop-2,3-dienoyl chloride[7] to furnish the required IMDAF substrate (**3**) (**Figure 2**).[8] On standing at room temperature, (**3**) slowly underwent cycloaddition, although the IMDAF was most conveniently carried out in refluxing toluene, when conversion was complete in less than 2 h. Analysis of the crude material by NMR showed the presence of single cycloadduct, the stereochemistry of which was initially tentatively assigned on the basis of coupling constants and n.O.e. difference studies to be that of the desired diastereoisomer (**4**).

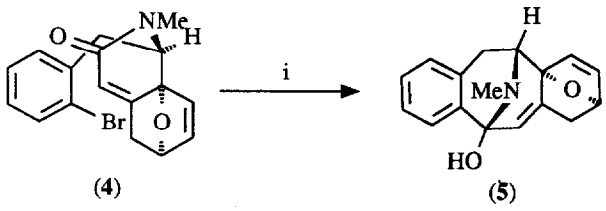


(2) (3) (4)

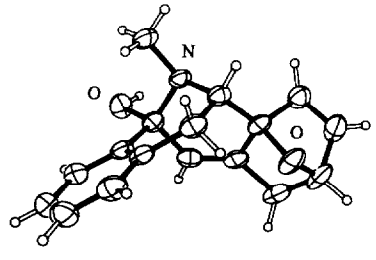
Reagents and conditions: (i) 2-$BrC_6H_5CH_2MgBr$, Et_2O, r.t., 54%; (ii) CH_2=C=CHCOCl, Et_3N, CH_2Cl_2, 40%; (iii) toluene, reflux, 2 h, quant.

Figure 2

Generation of the lithio- derivative of (**4**), by reaction with *n*-butyl-lithium, resulted solely in 1,2-addition to the amide carbonyl to give the aminol (**5**) (**Figure 3**), the structure of which was confirmed by X-ray crystallographic analysis.[9] This in turn permitted confirmation of the relative stereochemistry proposed for the IMDAF cycloadduct (**4**). The stereocontrol observed in the IMDAF can be rationalised by proposing that cycloaddition occurs *via* a conformation which places the 2-bromobenzyl group in the sterically least demanding *quasi*- equatorial position. All attempts to induce 1,4- addition, by generating the lithio- species in the presence of copper (I) salts, failed. Homolytic cleavage of the C-Br bond of (**4**) using $n$$Bu_3SnH$ in the presence of a catalytic quantity of AIBN in refluxing toluene resulted in the formation of a complex mixture of products.



(4) (5)



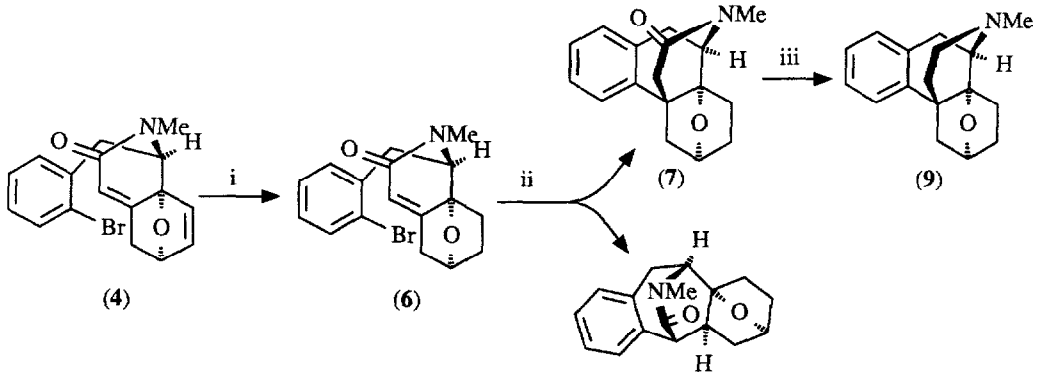
X-ray structure of (**5**)

Reagents and conditions: (i) *n*-BuLi, THF, -78°C, quant.

Figure 3

We reasoned that the unconjugated double bond of (**4**) was interfering with the radical mediated cyclisation. This double bond could be selectively hydrogenated using Wilkinson's catalyst and the reduced material (**6**) submitted to the same radical generation conditions which had been applied to (**4**) (**Figure 4**). Gratifyingly, this resulted in rapid disappearance of the starting material and clean conversion to a mixture of

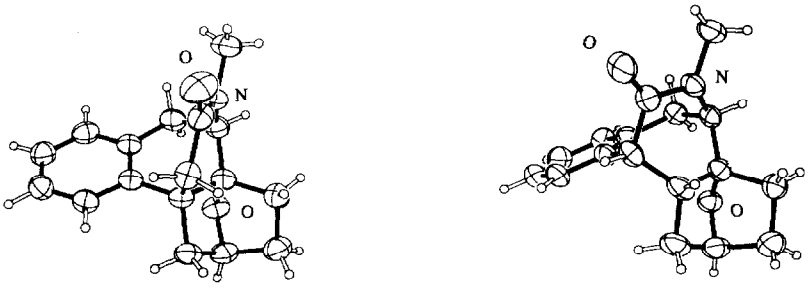
two isomeric products (*ca.* 2 : 3). Spectroscopic analysis of the purified materials permitted the minor, more polar product to be assigned the morphinan structure (**7**); with the less polar material being the regioisomeric product (**8**) resulting from radical addition to the less substituted position of the double bond.[8] The amide moiety of (**7**) which could be reduced (DIBAL, THF, -78°C → r.t.) to furnish (**9**) possessing the desired amine bridge structure of the morphinans.



Reagents and conditions: (i) $(Ph_3P)_3RhCl_2$, H_2, MeOH/toluene, quant; (ii) PhSnH, AIBN (cat.), C_6H_6, reflux, (**7**) 37% (**8**) 55%;(iii) DIBAL, THF, -78°C → r.t., quant.

Figure 4

Structures (**7**) and (**8**) were confirmed by X- ray crystallographic analysis (**Figure 5**).[9]



X-ray structure of (**7**)

Figure 5

X-ray structure of (**8**)

In summary, this Communication illustrates the utility of our tandem IMDAF / radical closure protocol for the rapid construction of complex polycyclic frameworks. Studies on the optimisation of the yield of the desired material in the radical cyclisation step are being undertaken at present and further synthetic results will be reported in due course.

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References

1. See L. M.Harwood, S. A. Leeming, N. S. Isaacs, G. Jones, J. Pickard, R. M. Thomas, and D. Watkin, *Tetrahedron Lett.*, 1988, **29**. 5017; L. M. Harwood, G. Jones, J. Pickard, R. M. Thomas, and D. Watkin, *Tetrahedron Lett.*, 1988, **29**, 5825 and references cited therein.

2. For a comprehensive review see: *"Opioid Analgesics - Chemistry and Receptors"*, A. F. Casy and R. T. Parfitt, Plenum, 1986.

3. For example see: M. Yoshida, Y. Hidaka, Y. Nawata, J. M. Rudziński, E. Osawa, and K. Kanematsu, *J. Amer. Chem. Soc.*, 1988, **110**, 1232; Y. Yamaguchi, K. Hayakawa, and K. Kanematsu, *J. Chem. Soc., Chem. Commun.*, 1987, 515; M. Yoshida, M. Hiromatsu, and K. Kanematsu, *J. Chem. Soc., Chem. Commun.*, 1986, 1168 and references cited therein.

4. T. Ghosh and H. Hart, *J. Org. Chem.*, 1988, **53**, 2396.

5. Radical mediated closures to generate quaternary centres have been reported; for instance see: G. Stork and N. H. Baine, *J. Amer. Chem. Soc.*, 1982, **104**, 2321.

6. R. H. Abu-Eittah and M. M. Hammed, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 844.

7. *"The Chemistry of Allenes"*, S. R. Landor, Vol. 1, Chapter 2.6, Academic Press, 1982.

8. All novel compounds isolated gave spectroscopic and analytical data in accord with their assigned structures. Selected data are as follows:

(**4**) ν_{max} (nujol®) 1689, 1631 cm^{-1}; δ_H (250 MHZ, $CDCl_3$) 2.21 (1H, dd, *J* 15Hz *J'* 1Hz), 2.47 (3H, s) 2.68 - 2.79 (1H, m), 3.02 (1H, dd, *J* 12Hz *J'* 10Hz), 3.27 (1H, dd, *J* 12Hz, *J'* 4Hz), 4.36 (1H, dd, *J* 10Hz, *J'* 4Hz), 5.24 (1H, dd, *J* 4Hz, *J'* 2Hz), 5.90 (1H, t, *J* 1Hz), 6.45 (1H, d, *J* 6Hz), 6.51 (1H, dd, *J* 6Hz, *J'* 2Hz); $^m/_z$ (E.I.) 346 ($M^{+\cdot}$), 176, 148, 110; m.p. (ether - CH_2Cl_2) 170 - 172°C,
(**5**) ν_{max} ($CHBr_3$) 3566, 2929 cm^{-1}; δ_H (250 MHZ, $CDCl_3$) 1.84 (1H, dd, *J* 12Hz *J'* 2Hz), 2.27 - 2.36 (4H, m) 2.19 - 3.14 (2H, m), 3.90 (1H, dd, *J* 8Hz *J'* 2Hz), 4.82 (1H, bs), 5.01 (1H, dd, *J* 4Hz, *J'* 2Hz), 5.49 (1H, m), 6.41 (1H, dd, *J* 6Hz *J'* 2Hz), 7.08 - 7.60 (4H, m); $^m/_z$ (C.I.) 268 (MH^+), 252, 250, 236, 192, 160, 144; m.p. (toluene - $CHCl_3$) 212 - 214°C,
(**7**) ν_{max} ($CHCl_3$) 3008, 1625 cm^{-1}; δ_H (500 MHZ, $CDCl_3$) 1.59 - 1.70 (2H, m), 1.81 - 1.77 (1H, m), 1.91 - 2.00 (1H, m), 2.27 - 2.33 (1H, m), 2.42 (1H, ddd, *J* 12Hz *J'* 6Hz *J''* 2.5Hz), 2.79 (1H, d, *J* 17Hz), 2.87 (1H, d, *J* 17Hz), 2.97 (3H, s) 3.06 (1H, dd, *J* 17Hz *J'* 2Hz), 3.25 (1H, dd, *J* 17Hz *J'* 4Hz), 3.90 (1H, t, *J* 3Hz), 4.67 (1H, t, *J* 5.5Hz), 7.01 - 7.22 (4H, m); $^m/_z$ (E.I.) 269 ($M^{+\cdot}$), 251, 240, 226, 211, 198, 184, 168, 155, 141, 128, 115, 84; m.p. (pentane - CH_2Cl_2) 211 - 212°C,
(**8**) ν_{max} ($CHCl_3$) 3000, 1656 cm^{-1}; δ_H (500 MHZ, $CDCl_3$) 1.36 - 1.41 (1H, m), 1.60 - 1.50 (2H, m), 1.69 (1H, dd, *J* 12Hz *J'* 8Hz), 1.86 - 1.97 (2H, m) 2.35 - 2.41 (1H, m) 3.08 (3H, s) 3.20 (1H, dd, *J* 17Hz, *J'* 4Hz), 3.33 (1H, dd, *J* 17Hz, *J'* 4Hz), 3.43 (1H, d, *J* 4.5Hz), 3.87 (1H, t, *J* 3.5Hz), 4.36 (1H, t, *J*5Hz), 6.97 - 7.18 (4H, m); $^m/_z$ (E.I.) 269 ($M^{+\cdot}$), 250, 212, 194, 144, 128, 115; m.p. (pentane - CH_2Cl_2) 235 - 236°C,

9. All X- ray crystallographic data were measured ($2\theta_{max}$ 110°) on a Nicolet R3m/V diffractometer using Cu-K_α radiation. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Centre. Any request should be accompanied by the full literature citation for this publication.

(**5**): Crystal data: $C_{17}H_{17}NO_2$; *M* = 267.3, monoclinic: $P2_1/c$, *a* = 6.697; *b* = 10.561; *c* = 19.046Å, *U* = 1337 $Å^3$, *Z* = 4, D_c = 1.328 g cm^{-3}, F(000) = 568. 1455 independent reflections with $I > 3\sigma(I)$ were used in the analysis. Final *R* = 6.00, final Hamiltonian weighted = 6.60.
(**7**): Crystal data: $C_{17}H_{19}NO_2$; *M* = 269.3, monoclinic : $C2/c$, *a* = 25.955; *b* = 6.476; *c* = 17.926 Å, *U* = 2678 $Å^3$, *Z* = 8, D_c = 1.336 g cm^{-3}, F(000) = 1152, μ(Cu-K_α) = 6.56 cm^{-1}. 1374 independent reflections with $I > 6\sigma(I)$ were used in the analysis. Final *R* = 1.6.
(**8**): Crystal data: $C_{17}H_{19}NO_2$; *M* = 269.3, triclinic : P1, *a* = 6.477; *b* = 9.706; *c* = 11.818 Å, *U* = 682 $Å^3$, *Z* = 2, D_c = 1.312 g cm^{-3}, F(000) = 288, μ(Cu-K_α) = 6.44 cm^{-1}. 1419 independent reflections with $I > 6\sigma(I)$ were used in the analysis. Final *R* = 2.04, final

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