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A DIELS-ALDER APPROACH TO FUNCTIONALISED *CIS*-HYDROISOQUINOLINES

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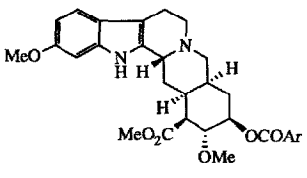
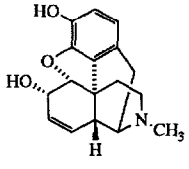
ABSTRACT: A new substituted 5,6-dihydro-2(1*H*)-pyridinone participates in highly efficient Diels-Alder reactions to give functionalised *cis*-hydroisoquinolines suitable for natural product synthesis.

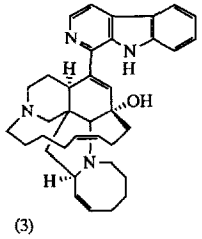
The *cis*-hydroisoquinoline ring system constitutes an important part of natural products such as the indole alkaloid reserpine (**1**). In addition, both *cis* and *trans* isomers have importance as synthetic intermediates in the synthesis of morphine alkaloids (e.g. morphine (**2**)), and their analogues, which are of considerable pharmacological interest. Most recently the isolation of the potent antileukemic alkaloid manzamine A (**3**) served to further focus our interest on the synthesis of highly substituted and functionalised *cis*-hydroisoquinolines.[1]



(1) Ar = 3,4,5-trimethoxyphenol

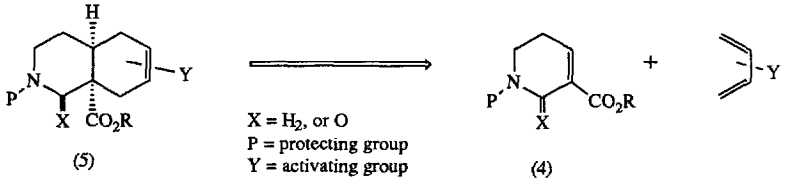


(2)



(3)

Recent approaches to this family of compounds include [3,3]sigmatropic rearrangements,[2] an asymmetric ring expansion reaction,[3] anionic and cationic ring forming or annulation procedures,[4] and the ubiquitous intramolecular Diels-Alder reaction.[5] We envisaged an alternative, very simple intermolecular Diels-Alder approach to these compounds, as outlined in Scheme 1.



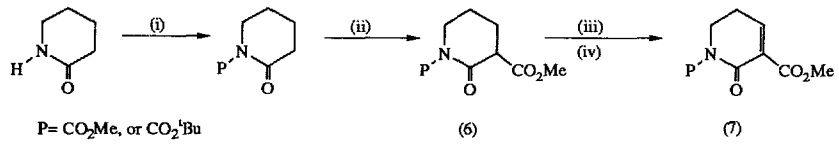
(5) (4)

Scheme 1

Such a route would have the advantage of a high degree of flexibility, due to the range of substituted and (particularly attractive) heterosubstituted dienes which could be used, leading to products having varied and useful functionality.

Thus, we initially hoped that a suitably protected tetrahydropyridine carboxylic ester (**4**, $X=H_2$) would participate in cycloadditions to give the desired products (**5**, $X=H_2$). Such a reaction would be particularly attractive since a suitable dienophile, arecoline (**4**, $X=H_2$, P=Me) is commercially available as the hydrobromide

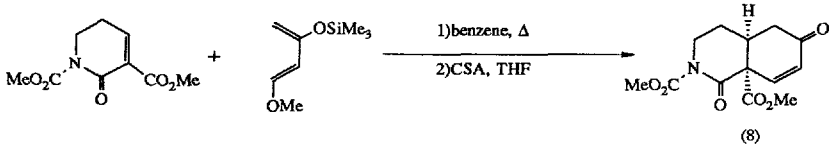
salt. However, preliminary attempts at Diels-Alder reactions using arecoline and the very reactive Danishefsky's diene (4-methoxy-2-trimethylsilyloxybutadiene) proved fruitless, and so we turned our attention to the alternative system (**4**, X=O). The required dihydropyridinone was prepared in good overall yield from δ-valerolactam as shown in Scheme 2.



Reagents
(i) NaH, $ClCO_2Me$, CH_2Cl_2 (65%), or $(Boc)_2O$, DMAP, CH_2Cl_2 (85%).
(ii) LDA, THF, $ClCO_2Me$ (70%).
(iii) NaH, THF, PhSeCl. (iv) H_2O_2, CH_2Cl_2 (92% overall).

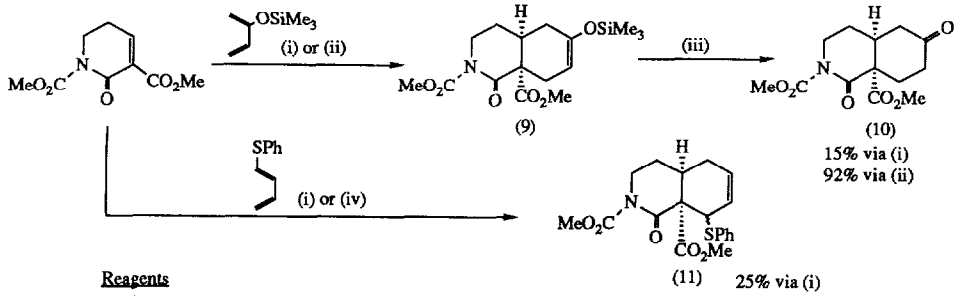
Scheme 2

Initial protection of the lactam NH as the methyl, or *tert*-butyl carbamate (subsequent chemistry has been carried out mainly with the methyl carbamate) was carried out straightforwardly, followed by *C*-carboxymethylation (LDA, THF, $ClCO_2Me$) to give (**6**). Subsequent introduction of the C3-C4 unsaturation was carried out via selenation (NaH, THF, PhSeCl), and immediate *syn*-elimination (CH_2Cl_2, H_2O_2, 0°C).[6] With (**7**) in hand we began our investigation of its Diels-Alder cycloadditions by reaction with Danishefsky's diene. Thus, brief heating of (**7**) with an excess of diene (2 eq.) at reflux in benzene, followed by treatment of the intermediate adduct with camphorsulphonic acid (CSA) in THF gave the expected product (**8**) in quantitative yield, Scheme 3.[7]



Scheme 3

Reaction of (**7**) with other, less reactive dienes under thermal conditions was, however, less successful, and so we turned to the possibility of using Lewis acid catalysis. We were very pleased to find that by simply stirring a mixture of (**7**) and 2-trimethylsilyloxybutadiene in CH_2Cl_2 at 0°C with $ZnBr_2$ an extremely clean cycloaddition process took place to give the silyl enol ether (**9**). This was subsequently treated with dilute HCl in THF to give ketone (**10**), the saturated analogue of the compound prepared previously, in 92% yield, Scheme 4.

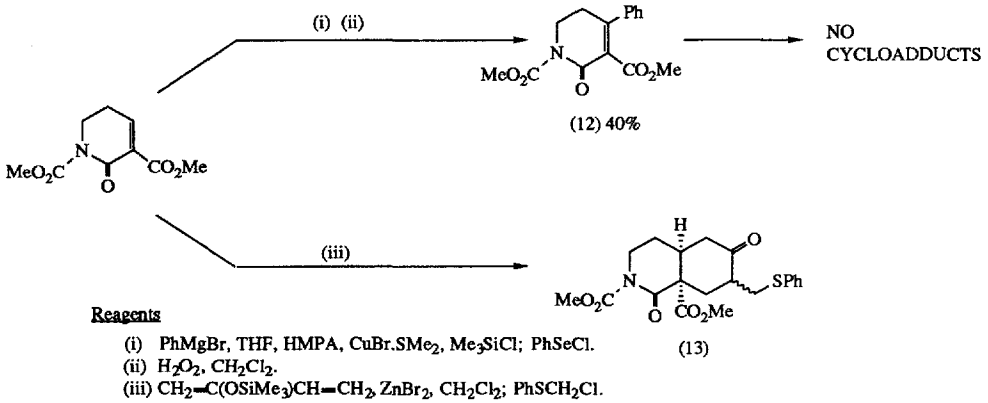


Reagents
(i) toluene, Δ.
(ii) $ZnBr_2$, CH_2Cl_2, 0°C, 1h.
(iii) HCl_{aq}
(iv) $ZnBr_2$, CH_2Cl_2, 0°C, 24h.

Scheme 4

This compares with a yield of only 15% of the same product when the reaction was carried out under thermal

conditions (toluene was necessary to effect any reaction).
The isolation of the intermediate silyl enol ether is potentially very useful, and indicates that a cycloaddition, rather than a Lewis acid mediated double-Michael process, is probably occurring. Under similar conditions the 4-phenylthiobutadiene also reacted smoothly to give the allylic sulphide (**11**) as a 1:1 mixture of diastereoisomers at C8, although here it was necessary to extend the reaction time considerably to 24 hours. Again, this procedure was preferable to the alternate, harsh conditions required to effect the thermal cycloaddition with this diene.
We later found that in the reaction of (**7**) with 2-trimethylsilyloxybutadiene equally good results could be obtained by the use of slightly less diene (1.5 eq.) and employing only a catalytic amount of $ZnBr_2$ (20 mol %).
These isoquinoline products are clearly quite well endowed with suitable substitution and functionality for further synthesis. However, we decided to investigate the possibilities for the introduction of additional carbon substituents at C4a and C7, which would have direct relevance to the morphine and manzamine skeletons, respectively.
We hoped that introduction of an aryl group at C4a would be possible by the use of an aryl-substituted analogue of (**7**) in the cycloaddition. A suitable compound (**12**) was prepared quite simply via conjugate addition of PhMgBr, followed by in-situ trapping with PhSeCl, and *syn*-elimination as before using H_2O_2. Unfortunately we were unable to effect cycloaddition reactions of (**12**) under any of the reaction conditions used previously.
More successful was the introduction of a CH_2SPh group at C7, which was effected in a one-pot procedure as indicated in Scheme 5.



Scheme 5

Thus simply adding $PhSCH_2Cl$ to the silyl enol ether (**9**) formed in situ as in Scheme 4, followed by stirring at room temperature for 3 hours gave the desired alkylated product (**13**) in 53% yield.
Both the high yields in the cycloadditions which furnish these functionalised hydroisoquinolines, and the readiness with which extra substituents can be introduced later, make this approach attractive for the synthesis of the basic manzamine skeleton. Our further efforts in this direction, including alternative elaboration of these products, and intramolecular versions of the Diels-Alder reactions will be reported later.

Acknowledgements
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References and Notes

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3. J. Aube, Tetrahedron Lett., 1988, **29**, 4509.
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5. S. Handa, K. Jones, C. G. Newton, and D. J. Williams, J. Chem. Soc., Chem. Commun., 1985, 1362; J. Levy, J-Y. Laronze, and J. Sapi, Tetrahedron Lett., 1988, **29**, 3303. An intramolecular Diels-Alder approach to the manzamine system has recently appeared, see K. M. J. Brands and U. K. Prandit, Tetrahedron Lett., 1989, **30**, 1423.
6. Data for (**7**): m.p. 51-53°C, υ_{max} (KBr) 3002, 2975, 1740, 1720, 1435, 1315, 1260, and 980 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 2.57 (2H, dt, J 4, 6 Hz), 3.84 (3H, s), 3.90 (3H, s), 3.98 (2H, t, J 6 Hz), and 7.56 (1H, t, J 4 Hz); δ_C (62 MHz, $CDCl_3$) 24.8, 43.5, 52.4, 54.1, 130.5, 149.5, 154.8, 159.8, and 164.4; Found M+, 213.0630; C, 50.47; H, 5,19; N, 6.51. $C_9H_{11}NO_5$ requires M 213.0637; C, 50.70; H, 5.20; N, 6.57%.
7. Data for (**8**): m.p. 83-84°C, υ_{max} (KBr) 3070, 3040, 3010, 2965, 2935, 1738, 1700, 1440, 1410, and 1258 cm^{-1}; δ_H (250 MHz, $CDCl_3$) 1.77-2.18 (2H, m), 2.41 (1H, dd, J 5, 16 Hz), 3.09 (1H, m), 3.60-3.72 (1H, m), 3.84 (3H, s), 3.90 (3H, s), 4.01 (1H, dt, J 6, 14 Hz), 6.20 (1H, d, J 10 Hz), and 6.92 (1H, dd, J 1.5, 10 Hz); δ_C (62 MHz, $CDCl_3$) 25.5, 36.6, 40.2, 45.4, 53.8, 54.4, 59.7, 130.44, 144.7, 154.4, 167.7, 169.5, and 195.4; Found M+, 281.0907; C, 55.55; H, 5.39; N, 5.2. $C_{13}H_{15}O_6N$ requires M 281.0899; C, 55.51; H, 5.38; N, 4.98%.
8. For related examples of Lewis acid mediated Diels-Alder reactions see P. J. Proteau and P. B. Hopkins, J. Org. Chem., 1985, **50**, 141; H-J. Liu and T. K. Ngooi, Can. J. Chem., 1984, **63**, 2676.

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