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Solution- and solid-phase synthesis of enantiomerically pure spiro oxindoles

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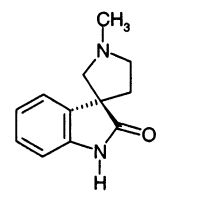
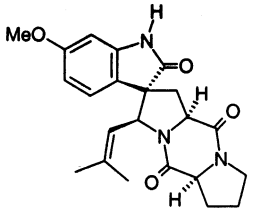
Abstract—A convenient synthesis of enantiomerically pure oxindoles using a three component reaction involving 1:3 dipolar cycloaddition reaction has been achieved using solution and solid phase chemistry.

In view of the fact that spiro oxindoles e.g. (**1**)[1] and (**2**)[2] exist in nature and several of them show significant biological activities we were interested to synthesize this class of compounds in enantiomerically pure form. Specifically we were interested to devise a simple and enantioselective synthesis of compounds represented by general structure (**3**).

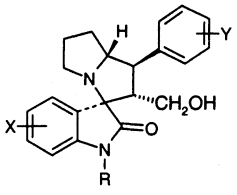
Structures represented by (**3**) have many desirable characteristics of drugs, i.e. molecular weights <500, presence of hydrogen bond acceptor and donor, aromatic rings which could be suitably substituted, a basic nitrogen which as a salt will impart solubility and overall condensed ring system which impart geometry that might be significant in drug discovery. In addition we



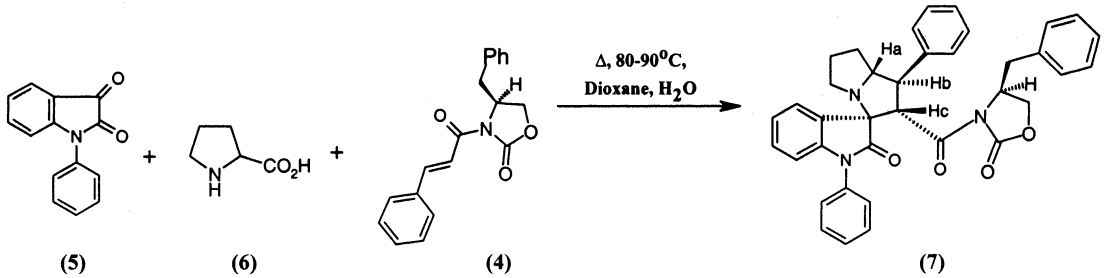
(1) (-) Horsfiline



(2) Spirotryprostatin A



(3)



(5) (6) (4) (7)

Scheme 1.

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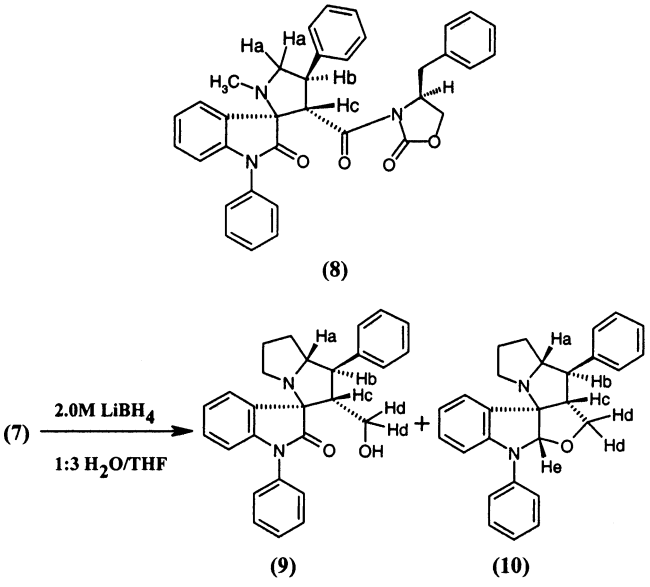
wanted to translate our solution chemistry into solid-phase and demonstrate that the optically active ligand used in the solid-phase could be recycled.

Based on the literature precedence[3] for the synthesis of racemates we envisaged that (**3**) could be synthesized using a three components reaction involving 1:3 dipolar cycloaddition reaction in which one of the components of course needs to be optically active. After investigating a couple of alternatives we found that compound (**4**) was best suited for our purpose. Compound (**4**) was prepared using Evans' chemistry from (*S*)-phenyl alaninol.

Thus, reaction of *N*-phenyl isatin (**5**) with proline (**6**) and (**4**) in aqueous dioxane at 80–90°C for 3 h yielded (**7**) (98%) as the only diastereoisomer (Scheme 1).

Compound (**7**)[4] was crystallized from ether–hexane, mp 195–196°C, $C_{37}H_{34}N_3O_4$ (M+H, 584.2552), $[\theta]_{222nm}$ = +322876, $[\theta]_{256nm}$ = −106667 and $[\theta]_{303nm}$ = +68791. In the NMR spectrum Ha appears at δ 4.56 (m), Hb at δ 4.09 (t, J = 9.3 Hz) and Hc at δ 4.96 (d, J = 9.3 Hz). The structure of (**7**) was unambiguously assigned based on X-ray crystallographic analysis (see Fig. 1).[5]



Scheme 2.

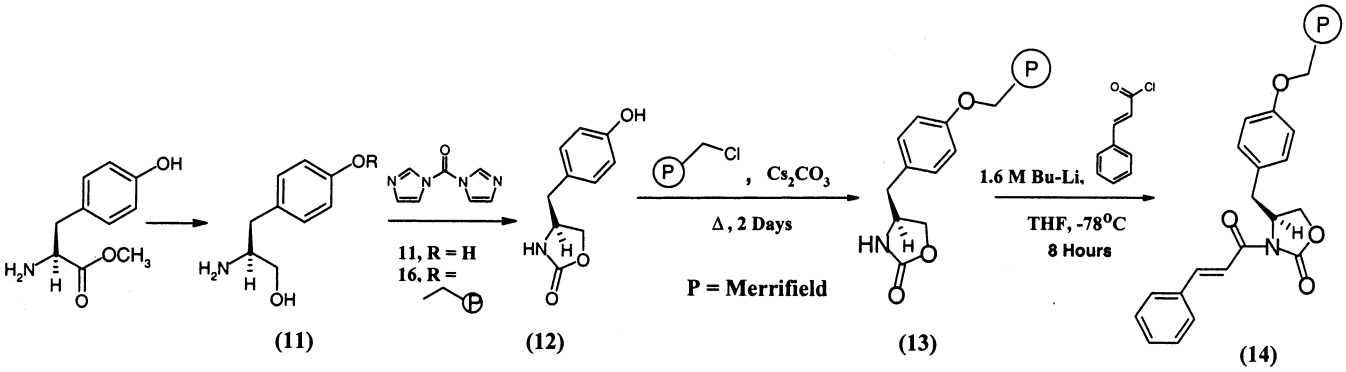
We repeated the above reaction with sarcosine to determine whether proline influenced the diastereoselectivity for the formation of (**7**) and obtained exclusively compound (**8**), mp 180°C, $C_{35}H_{31}N_3O_4$ (M+H, 558.2398), $[\theta]_{233nm}$ = +208902 and $[\theta]_{264nm}$ = −48400. In the NMR spectrum Ha appeared at δ 3.44 (2H, q), Hb at δ 4.6 (multiplet) and Hc at δ 4.83 (d, J = 8.7 Hz).

Reduction of (**7**) with excess lithium borohydride in aqueous tetrahydrofuran yielded a mixture of (**9**) (25%) and (**10**) (25%) (Scheme 2).

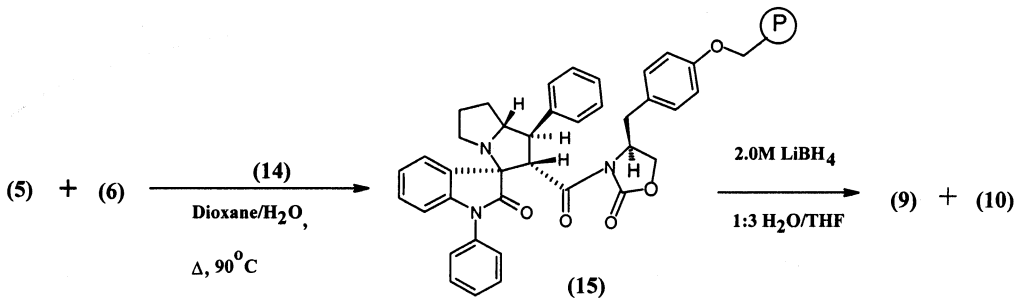
Compound (**9**), $C_{27}H_{26}N_2O_2$ (M+H, 411.2070), mp 147–149°C, $[\theta]_{234nm}$ = +53633 and $[\theta]_{285nm}$ = −11454. In the NMR spectrum of (**9**) measured in deuterated DMSO solution Ha appeared at δ 3.8 (octet), Hb at δ 3.1 which overlaps with one of the Hd protons, Hc at δ 3.25 (m), and Hd at δ 2.95 and δ 3.05, the hydroxyl group appears at δ 4.3 which couples to both the Hd protons (J = 3.5 Hz and 5.5 Hz). The spiro carbon atom appears at 72 ppm.

Compound (**10**), $C_{27}H_{26}N_2O$ (M+H, 395.2126), is a colorless crystalline solid, mp 156–158°C. In the NMR spectrum of (**10**)[4] He appears at δ 5.46 as a singlet.

Having had achieved solution-phase enantioselective synthesis of (**9**) and (**10**) we decided to translate it into solid-phase synthesis.[6] Thus, the oxazolidinone (**12**) prepared from L-tyrosine methyl ester via (**11**) was attached to Merrifield resin to yield (**13**) (Scheme 3). Resin bound (**13**) was converted to (**14**) as shown in Scheme 3. Suspension of (**14**) in aqueous dioxane was treated with proline (**6**) and *N*-phenyl isatin (**5**) and after heating the mixture at 80–90°C overnight it was filtered and the resin washed and dried. The resin containing the cycloaddition product (**15**) was reduced in aqueous tetrahydrofuran with lithium borohydride as described in solution chemistry. The above reaction was allowed to proceed overnight at room temperature and then filtered. Working up the filtrate yielded mainly (**9**) and a trace of (**10**) (Scheme 4) unlike in solution chemistry wherein they were produced in equal amounts. The resin (**16**) was washed thoroughly, dried and then suspended in tetrahydrofuran containing carbonyl di-imidazole and stirred at room temperature overnight. After filtration the resin was treated with



Scheme 3.



Scheme 4.

trifluoro acetic acid to yield (**12**) thus demonstrating that the optically active ligand could be recycled in our solid-phase synthesis (Scheme 4).

In summary, we have devised a convenient synthesis for preparing enantiomerically pure spiro oxindoles both in solution- and solid-phases. Obviously varying structures of the three components of the 1:3 cycloaddition reactions one should be able to create a significant library of compounds for biological testing.

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We wish to thank Professor K. Nakanishi and Dr. Gloria Proni of Columbia University for allowing us to make CD measurements in their laboratories. Two of us (N.S. and V.P.) would like to specially thank Schering–Plough Research Institute for awarding Industrial academic fellowships to work at Stevens Institute.

References

1. Palmisano, G.; Annusiata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *1*, 1.
2. (a) Danishefsky, S. J.; Von Nussbaum, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2175; (b) Williams, R.; Sebahar, P. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.
3. Fokas, D.; Ryan, W. Y.; Casebier, D. S.; Coffen, D. L. *Tetrahedron Lett.* **1998**, *39*, 2238.
4. All the compounds described in this paper were crystalline. Molecular weights were determined using high resolution mass spectrometry. NMR spectra were consistent with the assigned structures and further confirmed using NOE and HMBC experiments.
5. Compound **7**, mp 195–196°C, was crystallized from ether–hexane. Crystal data: $C_{37}H_{33}N_3O_4$, $M=583.69$, monoclinic, space group $P2_1$, $a=14.265(2)$, $b=10.241(1)$, $c=10.583(1)$ Å, $\beta=101.60(1)°$, $V=1514.5(6)$ Å^3, $Z=2$, $D_{calcd}=1.280$ g cm^{-3}, μ(Cu Kα radiation, $\lambda=1.5418$ Å)$=6.3$ cm^{-1}, crystal size: 0.24×0.20×0.10 mm. Intensity data (3290 non-equivalent $\pm h$, $-k$, $+l$ reflections, $\theta_{max}=75°$) were recorded at 296 K on an Enraf–Nonius CAD4 diffractometer. The crystal structure was solved by direct methods. Full-matrix least-squares refinement of atomic positional and thermal parameters (anisotropic C, N, O; fixed H contributions) converged (max. shift:esd = 0.03) at $R=0.041$ ($R_w=0.055$) over 2334 reflections with $I>2.0\sigma(I)$. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre, deposition number CCDC 188917. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
6. Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron Lett.* **2000**, *41*, 1265.

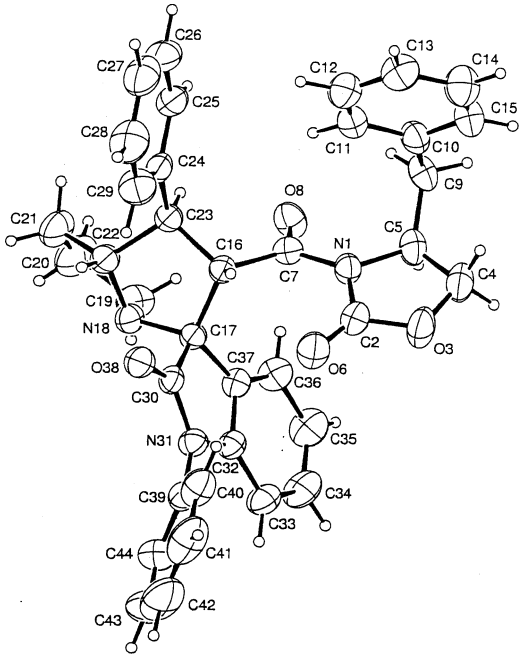

Figure 1. ORTEP diagram (40% probability ellipsoids) showing the crystallographic atom numbering scheme and solid-state conformation of compound **7**; small circles represent hydrogen atoms.