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Synthesis of spirooxindoles via asymmetric 1,3-dipolar cycloaddition

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Abstract—An efficient method was developed for the asymmetric synthesis of 2′-alkyl-4′aryl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-ones, which are potential inhibitors of the p53–MDM2 interaction. Our X-ray crystallographic analysis revealed that this 1,3-dipolar cycloaddition proceeds with high stereoselectivity but differently from previously published results.
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The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[1–4] For example, spirotryprostatin A (**1**), a natural product isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly;[4] and pteropodine (**2**) and isopteropodine (**3**) have been shown to modulate the function of muscarinic and serotonin receptors.[1] Recently, we have designed compound **4** containing the spirooxindole as the core structure as a potent non-peptide inhibitor of the p53–MDM2 interaction[5] (Fig. 1).

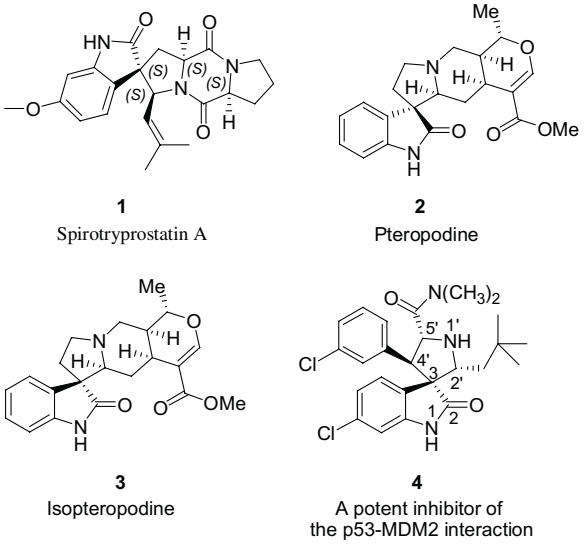

Figure 1. Representatives of spirooxindole-containing compounds.

Because of their remarkable biological activity, significant effort has been devoted to the stereoselective synthesis of substituted spirooxindole derivatives.[6–22] For example, Williams and co-workers have developed an efficient asymmetric synthesis of 2′,4′,5′-trisubstituted spirooxindoles (**8**) using (5*R*,6*S*)-5,6-diphenylmorpholin-2-one (**7**) as a chiral auxiliary (Scheme 1).[19–22] They have explored the reaction of active olefins with the asymmetric 1,3-dipolar intermediates formed by aldehydes and the morpholinone (**7**) to achieve 4′-carbalkoxyl-substituted 1*H*-spiro[indole-3,3′-pyrrolidin]-2-ones (**8**) (Scheme 1). To date, no synthesis of 2′-alkyl-4′-aryl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-ones has been reported, which is the core structure of our designed inhibitors of the p53–MDM2 interaction.[5] Herein, we report an asymmetric synthesis for this class of compounds.

First, the *E*-3-aryl-1,3-dihydro-indol-2-ones (**11**) were synthesized by condensation of oxindoles **9** with different aromatic aldehydes **10** under basic conditions either

Keywords: Spirooxindoles; Asymmetric 1,3-dipolar cycloaddition; Inhibitors of the p53–MDM2 interaction.
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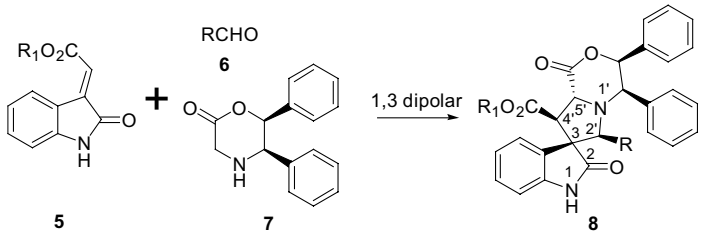
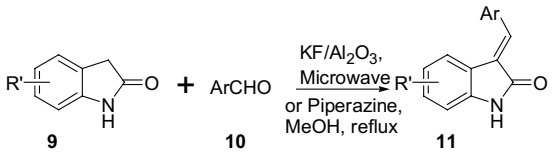


Scheme 1. Williams' asymmetric 1,3-dipolar cycloaddition method for synthesis of substituted spirooxindoles.

Table 1. Preparation of *E*-3-aryl-1,3-dihydro-indol-2-ones



Compound	R′	Ar	Yield (%)
11a	H	Phenyl	65[a]
11b	6-Br	Phenyl	60[a]
11c	6-CF_3	Phenyl	57[a]
11d	6-Cl	Phenyl	70[a]
11f	6-F	Phenyl	63[a]
11g	6-Cl	2-Pyridinyl	80[b]
11h	6-Cl	2-Thiophenyl	75[b]
11i	6-Cl	3-Methoxy-phenyl	60[a]

[a] KF/Al_2O_3, microwave, 60 W, 5 min.
[b] Piperazine, MeOH, reflux, 2–3 h.

in microwave[23] or under refluxation in MeOH (Table 1).[24] It was found that the latter condition gave better yield (Table 1), although a small amount of *Z*-isomer was observed. The crude products were used in a subsequent 1,3-dipolar cycloaddition without further purification. Compound **11a** was recrystallized from ethanol for X-ray crystallographic analysis and was confirmed as the *E* conformer (Fig. 2).

The asymmetric 1,3-dipolar cycloaddition was carried out by heating **11** with alkyl aldehydes **12** and (5*R*,6*S*)-5,6-diphenylmorpholin-2-one (**7**) in toluene in the presence of a dehydrating agent (Scheme 2). Compounds **13** were obtained as the major products with trace amount of other products observed by TLC. Compounds **13** were partially purified by silica gel column and were treated with 2 M dimethylamine in THF to afford amides **15** in good overall yield (Table 2).

In the previous studies,[19–22] it was reported that compounds **8** have the 2′*S*,3*S*,4′*R*,5′*R* absolute stereochemistry starting from the (5*R*,6*S*)-5,6-diphenylmorpholin-2-one **7** (Scheme 1). However, our X-ray crystallographic analysis of one important intermediate **14j** (Fig. 2) showed that the cycloaddition product **13** we obtained using the same chiral auxiliary **7** (Scheme 2) has the 2′*R*,3*S*,4′*R*,5′*R* absolute configuration. The mechanism of this unusual selectivity is not clear.

With the amides **14** in hand, removal of the chiral auxiliary by oxidization at 0 °C yielded the desired 2′,4′,5′-trisubstituted 1*H*-spiro[indole-3,3′-pyrrolidin]-2-ones (**15**)

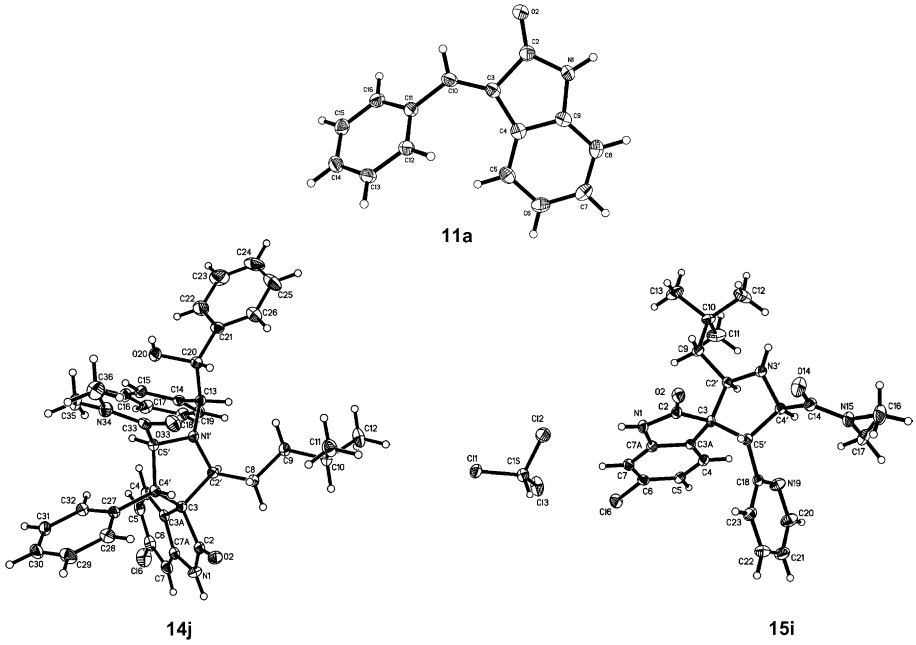
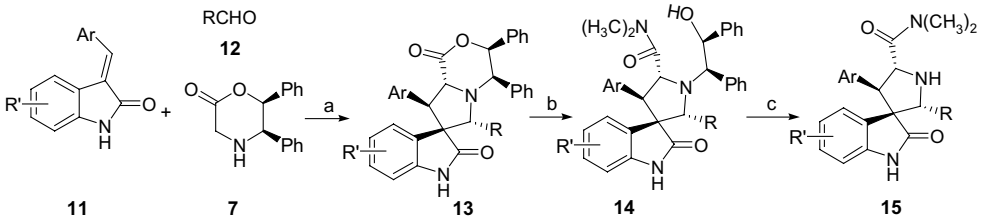


Figure 2. X-ray structures of compounds **11a**, **14j** and **15i**.



Scheme 2. Synthesis of 2′-alkyl-4′-aryl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-one. Reagents and conditions: (a) toluene, 4 Å molecular sieves, 70 °C, 5 h; (b) 2 M dimeylamine in THF, 8–0 h; (c) $Pb(OAc)_4$, MeOH–CH_2Cl_2, 0 °C.

Table 2. Summary of yield for intermediates **14** and the final target compounds **15**

Entry	R′	Ar	R	**14** (%)	**15** (%)
a	H	Phenyl	*i*-Butyl	70	55
b	6-Br	Phenyl	*i*-Butyl	75	62
c	6-CF_3	Phenyl	*i*-Butyl	75	59
d	6-Cl	Phenyl	*i*-Butyl	68	60
e	6-F	Phenyl	*i*-Butyl	73	58
f	6-Cl	2-Pyridinyl	2,2-Dimethyl-propyl	60	59
g	6-Cl	2-Thiophenyl	2,2-Dimethyl-propyl	65	63
h	6-Cl	3-MeO-phenyl	2,2-Dimethyl-propyl	75	65
i	6-Cl	Phenyl	2,2-Dimethyl-propyl	80	63
j	6-Cl	Phenyl	2-Dimethyl-butyl	78	60
k	6-Cl	Phenyl	*n*-Propyl	77	59

in 3–5 min. Higher temperature and/or longer reaction time led to some byproducts. The structures of target compounds **15** were determined by NMR and mass spectroscopy. The stereochemistry of the target compounds was further confirmed by X-ray crystallographic analysis of compound **15i** (Fig. 2).

In summary, using asymmetric 1,3-dipolar cycloaddition as the key step, 2′-alkyl-4′aryl-1*H*-spiro[indole-3,3′-pyrrolidin]-2-ones were efficiently synthesized as a novel class of inhibitors of the p53–MDM2 interaction. Analysis of a key intermediate (**14j**) and one final product (**15i**) by X-ray crystallography revealed that this 1,3-dipolar cycloaddition showed different stereoselectivity from that reported previously.[19–21]

References and notes

1. Kang, T.-H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *444*, 39–45.
2. Ma, J.; Hecht, S. M. *Chem. Commun.* **2004**, *10*, 1190–1191.
3. Edmondson, S.; Danishefsky, S. J.; Sepp-lorenzinol, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155.
4. Usui, T.; Kondoh, M.; Cui, C.-B.; Mayumi, T.; Osada, H. *Biochem. J.* **1998**, *333*, 543.
5. Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P., Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. *J. Am. Chem. Soc.*, in press.
6. Miyake, F. Y.; Yakushijin, K.; Horne, D. *Org. Lett.* **2004**, *6*, 711–713.
7. Takayama, H.; Fujiwara, R.; Kasai, Y.; Kitajima, M.; Aimi, N. *Org. Lett.* **2003**, *5*, 2967–2970.
8. Lizos, D. E.; Murphy, J. A. *Org. Biomol. Chem.* **2003**, *1*, 117–122.
9. Dornyei, G.; Incze, M.; Kajtar-Peredy, M.; Szantay, C. *Coll. Czech. Chem. Commun.* **2002**, *67*, 1669–1680.
10. Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826–14827.
11. Cochard, F.; Laronze, M.; Prost, E.; Nuzillard, J.-M.; Auge, F.; Petermann, C.; Sigaut, P.; Sapi, J.; Laronze, J.-Y. *Eur. J. Org. Chem.* **2002**, *20*, 3481–3490.
12. Selvakumar, N.; Azhagan, A. M.; Srinivas, D.; Krishna, G. G. *Tetrahedron Lett.* **2002**, *43*, 9175–9178.
13. Wang, X. Z.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4237–4240.
14. Cravotto, G.; Giovenzana, G. B.; Pilati, T.; Sisti, M.; Palmisano, G. *J. Org. Chem.* **2001**, *66*, 8447–8453.
15. Lizos, D.; Tripoli, R.; Murphy, J. A. *Chem. Commun.* **2001**, *24*, 2732–2733.
16. Syam Kumar, U. K.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 4193–4196.
17. Bagul, T. D.; Lakshmaiah, G.; Kawabata, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249–251.
18. Edmondson, S. D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138–1140.
19. Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.
20. Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137.
21. Sebahar, P. R.; Williams, R. M. *Heterocycles* **2002**, *58*, 563–575.
22. Overman, L. E.; Rosen, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4596–4599.
23. Villemin, D.; Martin, B. *Synth. Commun.* **1998**, *28*, 3201–3208.
24. Andreani, A.; Rambaldi, M.; Locatelli, A.; Bossa, R.; Galatulas, I.; NinciI, M. *Eur. J. Med. Chem.* **1990**, *25*, 187–190.