The remarkable effect of the 7-substituent in the diastereoselective oxidative rearrangement of indoles: Asymmetric synthesis of 3,3-disubstituted oxindoles†

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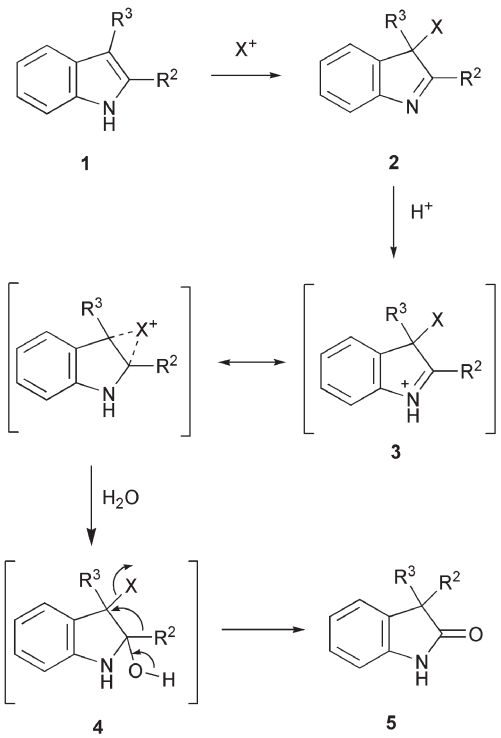
The nature of the 7-substituent has a remarkable effect on the diastereoselectivity of the oxidative rearrangement of indole-2-carboxamides derived from (*S*)-2-methoxymethylpyrrolidine into chiral 3,3-disubstituted oxindoles.

The construction of all carbon quaternary centres in an asymmetric manner remains a challenging problem in organic chemistry, not least because the process requires the creation of a new C–C bond at a hindered centre.[1,2] A number of elegant solutions to the problem have been advanced over the last few years and these are well illustrated by recent approaches to the synthesis of 3,3-disubstituted oxindoles. Such compounds are widely distributed in nature, and also serve as starting points for the synthesis of more complex indole alkaloids. Thus, for example, approaches based on the construction of the oxindole ring itself employing the asymmetric Heck reaction have been developed,[3] as have those that use an asymmetric functionalization of an existing oxindole.[4–8] Asymmetric variants on the Black rearrangement[9] have also been used; these feature the rearrangement of a 3-substituted-2-alkoxycarbonyloxyindole catalyzed by a chiral derivative of DMAP.[10,11] We now report an alternative approach to the asymmetric synthesis of 3,3-disubstituted oxindoles using an oxidative rearrangement of an indole-2-carboxamide bearing a chiral auxiliary, in which the nature of the substituent at the apparently remote indole 7-position plays a major, but totally unexpected, role.

The oxidative rearrangement of indoles to oxindoles upon treatment with electrophilic halogenating agents has long been known. Although the reaction has been investigated in simple indoles,[12–14] it has also found use in indole alkaloids,[15,16] and has recently been elegantly employed in a biogenetically patterned transformation of the *Corynanthe* skeleton into the *Strychnos* system.[17] The generally accepted mechanism is shown in Scheme 1 and involves conversion of the indole **1** into the 3-haloindolenine **2**, followed by protonation to give cation **3**, possibly stabilized by the cyclic halonium ion, attack of a nucleophile (water) and finally migration of the R^2-group with loss of halide and formation of the oxindole **5**.



Scheme 1

In connection with our efforts directed towards the total synthesis of diazonamide A (Fig. 1),[18,19] we were attracted to the oxidative rearrangement of indoles for the construction of the C-10 quaternary centre (diazonamide A numbering), and wondered if an asymmetric variant could be developed by employing a chiral

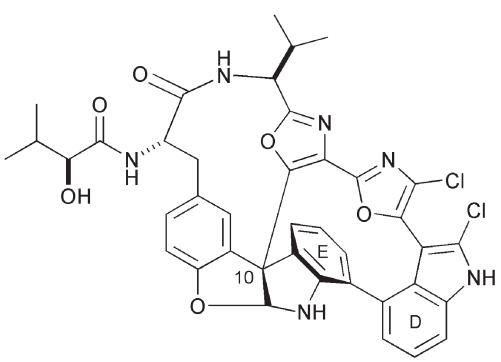


Fig. 1 Diazonamide A

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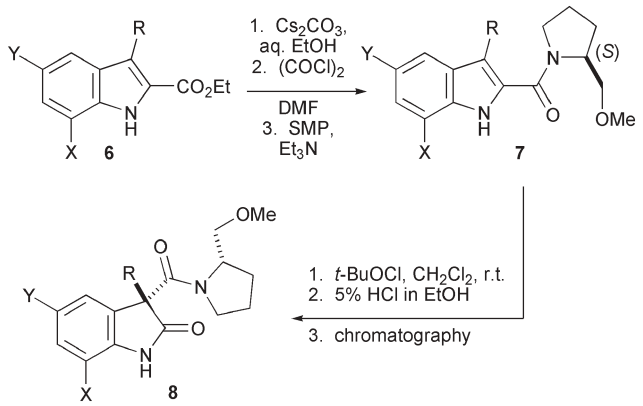
† Electronic supplementary information (ESI) available: General experimental details, characterization data for chiral oxindoles **8**, X-ray crystal structures of **8f** and **8g**. See DOI: 10.1039/b613716d



Scheme 2

Table 1 Diastereoselective oxidative rearrangement of indoles **7** into oxindoles **8**

6–8	X	Y	R	**8** Yield (%)	dr
a	H	H	Ph	82	1.3 : 1
b	Br	H	Ph	83	8 : 1
c	Br	H	4-Cl–C_6H_4	82	9.5 : 1
d	H	Br	Ph	93	1.4 : 1
e	H	Br	4-Cl–C_6H_4	90	1.4 : 1
f	Cl	H	Ph	91	6 : 1
g	F	H	Ph	95	2 : 1
h	Ph	H	Ph	75	11 : 1
i	Br	H	Me	90 (65)	4 : 1 (15 : 1 at 0 °C)

auxiliary at the indole 2-position (**1**, R^2 = chiral auxiliary). The chiral auxiliary investigated was (*S*)-2-methoxymethylpyrrolidine (SMP), one of the most generally useful auxiliaries that has been used in a very wide range of different applications.[20]

Thus a range of indole-2-carboxylates **6**, prepared by the Fischer indole synthesis, was converted into the corresponding (*S*)-2-methoxymethylpyrrolidinamides **7**, which were subjected to oxidative rearrangement using *tert*-butyl hypochlorite as the halogen source and HCl in ethanol to initiate the rearrangement.[14] The oxindoles **8** were obtained in good to excellent yield after chromatography (Scheme 2, Table 1) as a mixture of two diastereoisomers due to the presence of the new chiral quaternary centre. The first result was disappointing, the oxindole **8a** being formed as a *ca.* 1.3 : 1 mixture. However, since our projected diazonamide synthesis required a suitable substituent that would enable formation of the rings E–D biaryl bond at a later stage, we investigated the corresponding 7-bromoindole **7b**. Gratifyingly, the oxindole **8b** was formed as a 8 : 1 mixture of diastereoisomers. The major diastereoisomer was isolated by crystallization, and subsequent X-ray crystallographic analysis allowed the configuration of the new chiral centre to be assigned as (*S*) (Fig. 2).[21] The corresponding 4-chlorophenyl derivative **7c** behaved similarly. Hence the presence of the bromine substituent at the indole 7-position appears to have a dramatic effect on the stereochemical course of the oxidative rearrangement. That it is the 7-position that is important was established by studies on the 5-bromoindoles **7d,e** that gave the corresponding oxindoles with poor diastereoselectivity (Table 1). Stereoselectivity was restored in the rearrangement of the 7-chloro- and 7-fluoroindoles **7f** and **7g**, although the levels of selectivity were more modest. Nevertheless the major

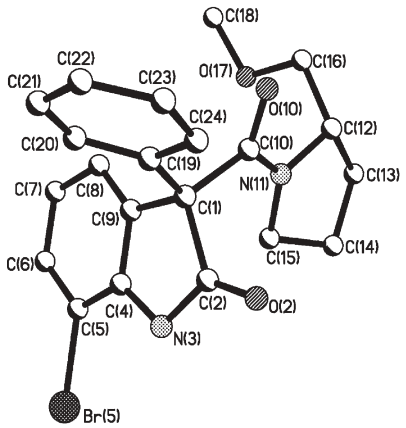


Fig. 2 X-Ray crystal structure of oxindole **8b**.

diastereoisomers of oxindoles **8f** and **8g** could again be isolated by crystallization, and their stereochemistry confirmed by X-ray analysis (see ESI†). Further evidence that the effect of the indole 7-position was purely steric was obtained in the oxidative rearrangement of the 7-phenylindole **7h** that gave an 11 : 1 ratio of oxindole products **8h**. Finally it was demonstrated that the effect was not limited to 3-arylindoles, and the 7-bromo-3-methylindole SMP-derivative **7i** gave a 4 : 1 ratio of oxindoles **8i**, a ratio that was increased to 15 : 1 when the acid catalyzed rearrangement step was carried out at 0 °C rather than at room temperature. Again the major diastereoisomer of oxindole **8i** was readily obtained by crystallization, and X-ray analysis established its stereochemistry (Fig. 3).[21]

Hence the presence of a large substituent at the indole 7-position has a dramatic effect on the stereoselectivity of the oxidative rearrangement of the indoles **7**. The influence of a substituent at a seemingly remote position on the stereochemical outcome of an auxiliary mediated reaction is truly remarkable and extremely unusual. Therefore we sought some evidence for the exact nature of this process. It was clear from NMR spectroscopy that the initial chlorination step was poorly stereoselective. Thus chlorination of both **7b** and **7i** at room temperature gave an isolable

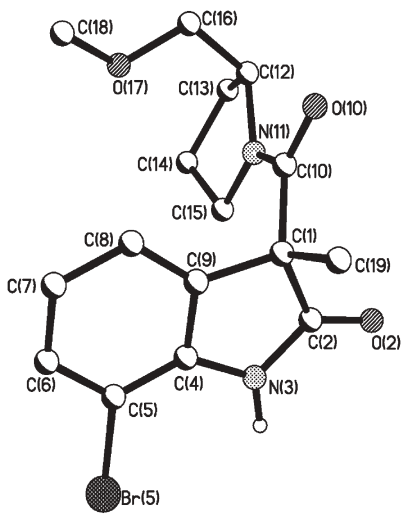
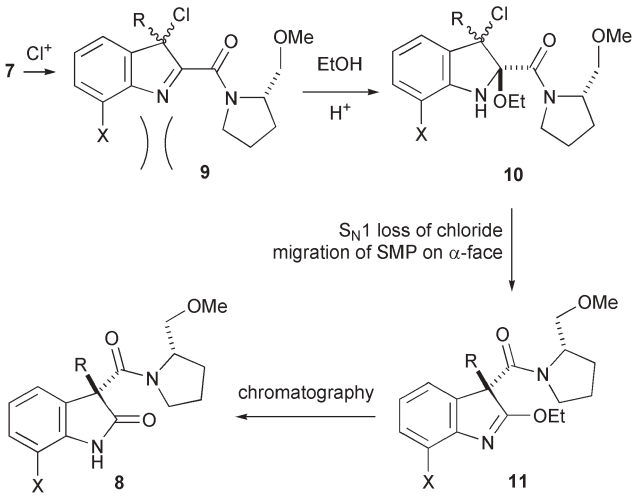


Fig. 3 X-Ray crystal structure of oxindole **8i**.



Scheme 3

3-chloroindolenine intermediate **9** (X = Br, R = Ph or Me) as a 1.4 : 1 mixture of diastereoisomers. It is in this intermediate that we assume that the 7-substituent plays a role by severely limiting the conformational mobility of the 2-methoxymethylpyrrolidine group. Inspection of molecular models suggests that the conformation depicted in Scheme 3 would minimize steric interaction both with the newly introduced chlorine and the large substituent at C-7. Protonation at nitrogen followed by auxiliary-controlled attack of ethanol from the least hindered side would then lead to intermediate **10**, whereupon S_N1 loss of chloride with concomitant migration of the auxiliary across the α-face would give 2-ethoxyindolenine **11** in which the stereochemistry of the final product is already established before hydrolysis to the oxindole **8** upon chromatography. In accord with our proposal, in the case of the oxidative rearrangement of 7-bromoindole **7b**, we were able to isolate the ethoxyindolenine **11** (X = Br, R = Ph) and ascertain that it was an 8 : 1 mixture of diastereoisomers. An alternative explanation is that the α- and β-chloro epimers of indolenine **9** are in equilibrium *via* the *N*-chloroindole as has been suggested in simpler systems,[22] with the equilibration possibly being assisted by the presence of a substituent X, and it is the β-chloro compound, with the chloride *anti* to the migrating group, that reacts faster.

The applications of this remarkable effect of a remote substituent in the asymmetric synthesis of a range of 3,3-disubstituted oxindoles are under investigation.

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21 Full hemisphere of data collected, corrected for Lorentz and polarization and for absorption, using multiple equivalent reflections. Refinements on F^2 using SHELXTL. Compound **8b** (crystallizes with two independent molecules in the asymmetric unit and with 0.5 mol $CHCl_3$): Rigaku MM007 high brilliance generator, confocal optic, Saturn 92 detector, colourless needle 0.2 × 0.01 × 0.01 mm, $C_{21.5}H_{21.5}BrCl_{1.5}N_2O_3$, M_r = 488.99, monoclinic, space group *P*2(1), a = 9.64370(19), b = 12.4445(12), c = 18.3737(17) Å, β = 102.099(3)°, V = 2156.1(3) Å^3, Z = 4, $2\theta_{max}$ 136° , CuKα λ = 1.54718 Å, T = 173(2) K, ρ_{calcd} = 1.506 g cm^{-3}, μ = 4.520 mm^{-1} (max, min transmission 1.00, 0.3940), 28203 reflections collected, 7217 unique [$R_{(int)}$ = 0.1652], R_1 = 0.0858, $wR2$ = 0.1330 for 4900 observed reflections [$(I) > 2\sigma(I)$], max. and min. residual electron density 0.494, −0.481 e Å^{-3}. Flack parameter 0.01(3). Compound **8i** Rigaku MM007 high brilliance generator, confocal optics, Mercury detector, colourless prism 0.1 × 0.03 × 0.03 mm, $C_{16}H_{19}Br_1N_2O_3$, M_r = 367.24, orthorhombic, space group $P2_12_12_1$, a = 8.5669(14), b = 12.7503(16), c = 14.900(3) Å, V = 1627.6(4) Å^3, Z = 4, $2\theta_{max}$ 50.7° , MoKα λ = 0.71073 Å, T = 93(2) K, ρ_{calcd} = 1.499 g cm^{-3}, μ = 2.539 mm^{-1} (max., min. transmission 1.00, 0.7533), 10 463 reflections collected, 2932 unique [$R_{(int)}$ = 0.0274], R_1 = 0.0206, $wR2$ = 0.0468 for 2707 observed reflections [$(I) > 2\sigma(I)$], max. and min. residual electron density 0.589, −0.294 e Å^{-3}. Flack parameter −0.005(7). CCDC 609781–609784. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613716d.
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