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Studies on the Enantiospecific Synthesis of Oxindole Alkaloids

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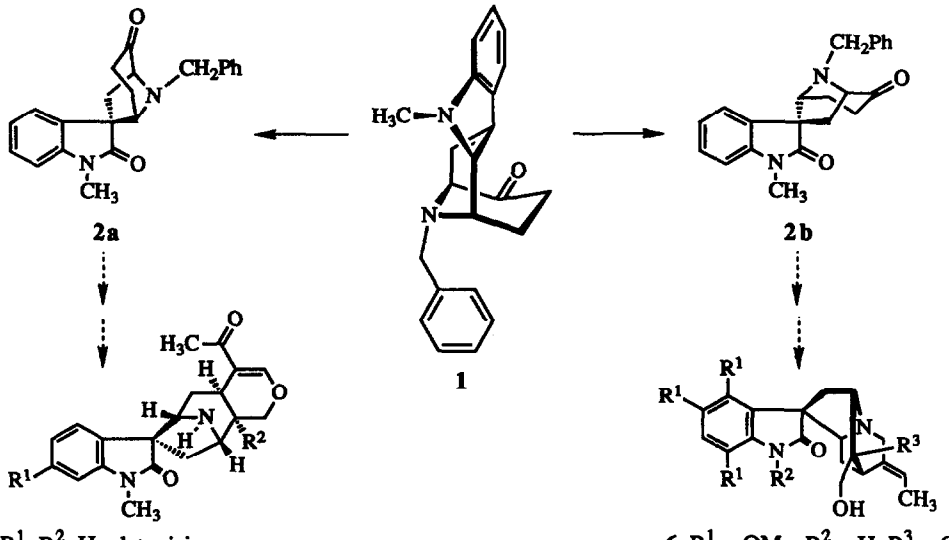
*Abstract: The optically active N_a-methyl, N_b-benzyltetracyclic ketone **1** was converted into either diastereomeric spirocyclic oxindole **2a** (91:9) or **2b** (97:3) with high diastereoselectivity on prudent choice of osmium reagents. Oxindole **2a** is now available in enantiospecific form for the synthesis of Alstonia alkaloids while diastereomer **2b** can be employed for the preparation of Gardneria and Voacanga bases.*

Several oxindoles which contain the azabicyclo[3.2.1]nonane ring system have been reported in recent years.[1] Alstonisine **3**, isolated from *Alstonia muelleriana* Domin by Elderfield and coworkers,[1b] is characteristic of oxindoles which have been obtained from *Alstonia* species. The structure of this alkaloid was established through single crystal X-ray analysis by Nordman.[2] Unfortunately this base was depicted incorrectly in that report. In 1978 Le Quesne and coworkers determined the correct absolute configuration of

Figure 1



3 R^1=R^2=H; alstonisine
4 R^1=OMe, R^2=H; N_b-demethylalstophylline oxindole
5 R^1=OMe, R^2=OH; 16-hydroxy-N_b-demethylalstophylline oxindole

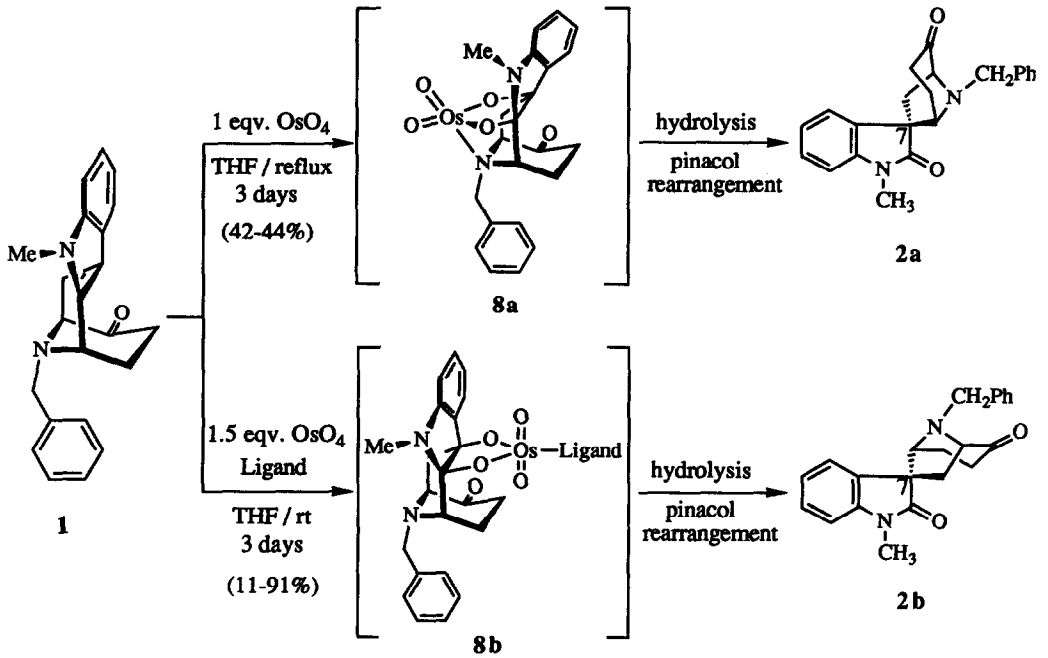
6 R^1 = OMe, R^2 = H, R^3 = OH; chitosenine
7 R^1 = H, R^2 = Me, R^3 = CO_2Me; voachalotine oxindole

oxindole **3** by a biomimetic transformation into talpinine.[3] The related *Alstonia* alkaloids **4** and **5** were recently isolated,[1c,d] and their configurations were established by NOE spectroscopic experiments. Interestingly the oxindoles **6**, isolated from *Gardneria multiflora* Makino,[1e] and **7** (from *Voacanga chalotiana* Pierre ex Stapf[1f]) contain a spirocyclic ring juncture at C(7) which is opposite in configuration to alkaloids **3-5**.

Few methods for the stereoselective synthesis of oxindoles are currently available, although progress has been made recently.[4] Diastereoselective preparation of oxindole **2a** or **2b** from the common intermediate ketone (-)-**1** would provide a potential route for the enantiospecific total synthesis not only of the *Alstonia* oxindoles **3-5** but also of the *Gardneria* oxindoles (see **6**), as well as the *Voacanga* base **7**. The tetracyclic ketone **1** is available in enantiospecific fashion on large scale *via* methods developed in this laboratory.[5] This ketone has been exploited as a common intermediate for the total synthesis of a number of macroline/sarpagine/ajmaline-related indole alkaloids.[6]

In earlier work it was found that the N_a-H, N_b-benzoyltetracyclic ketone was transformed in diastereoselective fashion into the corresponding oxindole in 88% yield by the action of *t*-butyl hypochlorite.[7] Treatment of the N_a-methyl, N_b-benzoylderivative of **1** under the same conditions, however, did not provide any detectable oxindole. Hence, a different method was required for the preparation of N_a-methyl oxindoles from their corresponding N_a-methyl indoles. Initially, the conversion of tetracyclic ketone **1** into oxindole **2** was attempted with osmium tetroxide under the conditions of Sakai *et al.*[8] (Scheme 1). This produced

Scheme 1



oxindoles **2a** and **2b** in a 1:1 ratio in low yield (Table 1, entries 3 and 10). The lack of diastereoselectivity with the OsO_4/pyridine mixture prompted a change in reagent. A larger aminoligand, such as quinuclidine,[9] was chosen to improve the diastereoselectivity in this process. Indeed, treatment of ketone **1** in THF with osmium tetroxide in the presence of three equivalents of quinuclidine gave a 3:1 ratio of oxindoles **2b**:**2a**, albeit in low yield. The commercially available *Cinchona* alkaloid derivatives developed by Sharpless and coworkers were then utilized as ligands.[10] Initially, it was hoped that these dihydroquinine and

Table 1. Results from the Treatment of Tetracyclic Ketone **1** with Osmium Reagents.[a]

Entry	Ketone[b]	Ligand[c]	eqv. OsO_4	Temp, °C	Time	Oxindole	Yield, %	**2a:2b**
1	(±)-**1**		1.0	reflux	3 d	(±)-**2**	44	91:9
2	(±)-**1**		3.0	reflux	3 d	(±)-**2**	32	50:50
3	(±)-**1**	pyridine	1.5	rt	3 d	(±)-**2**	36	50:50
4	(±)-**1**	quinuclidine	1.5	rt	3 d	(±)-**2**	11	25:75
5	(±)-**1**	DHQ	1.5	rt	3 d	(±)-**2**	82	24:76
6	(±)-**1**	DHQD	1.5	rt	3 d	(±)-**2**	76	48:52
7	(±)-**1**	$(DHQ)_2PHAL$	1.5	rt	3 d	(±)-**2**	76	20:80
8	(±)-**1**	$(DHQD)_2PHAL$	1.5	rt	3 d	(±)-**2**	66	47:53
9	(-)-**1**		1.0	reflux	3 d	**2**	42	91:9
10	(-)-**1**	pyridine	1.5	rt	3 d	**2**	36	50:50
11	(-)-**1**	DHQ	1.5	rt	3 d	**2**	91	3:97
12	(-)-**1**	DHQD	1.5	rt	3 d	**2**	77	20:80
13	(-)-**1**	$(DHQ)_2PHAL$	1.5	rt	3 d	**2**	81	25:75
14	(-)-**1**	$(DHQD)_2PHAL$	1.5	rt	3 d	**2**	82	20:80

[a]Reactions conducted in THF under a nitrogen atmosphere. [b]Racemic ketones unless otherwise noted. [c]Ligands: DHQ = dihydroquinine 4-chlorobenzoate[10]; DHQD = dihydroquinidine 4-chlorobenzoate[10]; $(DHQ)_2PHAL$ = dihydroquinine 1,4-phthalazinediyl diether[10]; $(DHQD)_2PHAL$ = dihydroquinidine 1,4phthalazinediyl diether[10].

dihydroquinidine based ligands would permit selective formation of either diastereomeric oxindole **2a** or **2b**. Unfortunately, all of the *Cinchona* derived ligands which were utilized preferentially furnished oxindole **2b** over diastereomer **2a** whether (±) or optically active ketone **1** was employed. In the best case, treatment of optically active ketone (-)-**1** with OsO_4/ dihydroquinine 4-chlorobenzoate[10] gave oxindole **2b** in 94% de in 91% yield (Table 1, entry 11).

It is felt that attack of the OsO_4/ligand complex occurred preferentially on the indole 2,3-double bond from the least hindered β-face of ketone **1** to produce an intermediate such as **8b** (Scheme 1). This osmate ester complex **8b** was subsequently hydrolyzed to the corresponding cis-diol[8c] on the addition of *aq.*

$NaHSO_3$ to the reaction mixture. The cis-diol then underwent a pinacol rearrangement to provide oxindole **2b**, accompanied by only traces of **2a**. This oxindole **2b** was purified readily by flash chromatography.

In an effort to prepare oxindole **2a**, a solution of ketone (-)-**1** in THF was stirred with OsO_4 at 0 °C for one hour in the absence of other ligands. The mixture which resulted was then heated at reflux for 3 days. Hydrolysis with *aq*. $NaHSO_3$, which was followed by flash chromatography, provided a 91:9 ratio of oxindoles **2a**:**2b** in 42-44% yield (Table 1, entries 1 and 9). Again oxindole **2a** was readily separated from **2b** by flash chromatography.

In an effort to rationalize this complete reversal in stereoselectivity, it is believed in the latter case that OsO_4 first coordinates to the N_b-piperidine nitrogen function (see **8b**) which facilitates intramolecular attack of the osmium reagent on the α-face of the indole 2,3-double bond to generate osmium intermediate **8a**. Hydrolysis of **8a** (*aq*. $NaHSO_3$) followed by a pinacol rearrangement then provided diastereomeric oxindole **2a**.

In summary, the synthesis of either diastereomeric oxindole **2a** or **2b** has been accomplished with excellent diastereoselectivity from the common intermediate (-)-**1**. These results provide a route for the enantiospecific total synthesis of *Alstonia* oxindoles **3**-**5** (from **2a**), while diastereomer **2b** can be employed for the construction of the rigid azabicyclo[3.2.1]nonane ring systems of the *Gardneria* and *Voacanga* alkaloids. Further work in this area will be reported in due course.

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