Studies Directed toward the Enantiospecific Synthesis of *Gardneria*, *Voacanga*, and *Alstonia* Oxindole Alkaloids[1]

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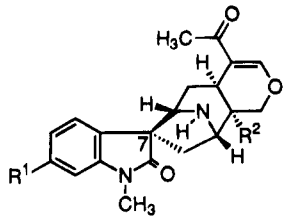
A method has been developed to convert N_a-methylmacroline-related indoles into their corresponding oxindoles with a high degree of diastereoselectivity. Prudent choice of the osmium reagent led to the stereoselective conversion of (−)-5-methyl-9-oxo-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (**14a**) into either diastereomeric N_b-benzyltetracyclic oxindole **21a** or **24a**. Treatment of racemic or (−)-N_b-benzyl ketone **14a** with osmium tetraoxide in the absence of amino ligands led to the oxindole **21a** with the same configuration about the spiro juncture at C(7) as the *Alstonia* oxindole alstonisine (**1**) with 10:1 diastereoselectivity, whereas the oxindole **24a** with the opposite configuration was obtained diastereoselectively in greater than 91% yield when ketone **14a** was treated with osmium tetraoxide in the presence of quinuclidine ligands. This conversion was found to be almost completely diastereoselective (94% de) to give oxindole **24a** when dihydroquinine 4-chlorobenzoate (DHQ-CLB) was employed as the ligand. Tranformation of the N_b-methyltetracyclic ketone **14b** produced the oxindole **24b** which also possessed the configuration opposite to that of alstonisine (**1**) at the spirocyclic carbon [C(7)] under all reaction conditions investigated to date. Oxindoles **24a** and **24b** can be employed for the enantiospecific preparation of *Gardneria* and *Voacanga* oxindole bases. In addition, oxindole **21a** is now available for the enantiospecific synthesis of *Alstonia* oxindole alkaloids.

Introduction

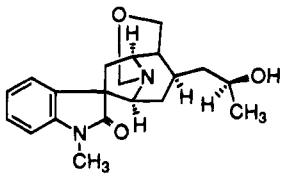
Elderfield and Gilman reported the isolation of the first macroline-related oxindole alkaloid from *Alstonia muellerlana* Domin and termed it alstonisine (**1**).[2] The



1 $R^1 = R^2 = H$; alstonisine

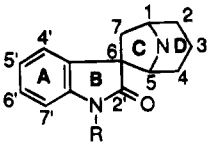
2 $R^1 = OMe$, $R^2 = H$;
N_b-demethylalstophylline oxindole

3 $R^1 = OMe$, $R^2 = OH$;
16-hydroxy-N_b-demethylalstophylline oxindole



4 macroxine

oxindole nature of this base was apparent from UV and IR spectroscopy;[2] however, the structure of this alkaloid remained unknown until its single crystal X-ray analysis by Nordman in 1963.[3] Unfortunately, an error in transposition of the structure to paper in this earlier report has resulted in an incorrect representation of the structure of alstonisine **1**.[3] The correct absolute configuration of alstonisine **1** at C(3), C(5), C(15), and C(16) was later determined by a biomimetic transformation of oxindole **1** into talpinine by Le Quesne;[4] however, direct confirmation of the stereochemistry at the spirocenter [C(7)] has not been reported. This constitutes one of the principle reasons for interest in the enantiospecific total synthesis of this base. Since this initial report, alstonisine **1** has also been isolated from *Alstonia angustifolia* Wall.[5] Several other macroline-related oxindole alkaloids have recently been isolated from *Alstonia macrophylla* Wall including N_b-demethylalstophylline oxindole (**2**),[6] 16-hydroxy-N_b-demethylalstophylline oxindole (**3**),[7] and macroxine (**4**).[8] The configuration of oxindole alkaloids **2** and **3** at C(7) has been determined by NOE spectroscopic experiments.[6,7] All of the macroline-related oxindole alkaloids **1**–**4** contain the 8-azabicyclo[3.2.1]nonane substructure represented in oxindole **5**.[9]



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Biogenetic considerations suggest that the indole alkaloid alstonerine **6** may serve as a precursor to alstonisine (**1**).[4] It is unclear whether oxindoles such as **1**–**4** serve a specific function in *Alstonia* species[10] or are simply present as metabolites. Although none of the *Alstonia* oxindoles **1**–**4** have been tested biologically in detail, at least one spirocyclic oxindole analog that contains the substructure **5** has found medicinal importance. Sakai and co-workers have employed spirocyclic

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(1) For a preliminary account of part of this work, see: (a) Peterson, A. C.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 2651. (b) Peterson, A. C.; Cook, J. M. *Abstracts of Papers*, 1994 Joint Central/Great Lakes Regional ACS Meeting, Ann Arbor, MI, June 1–3, 1994; American Chemical Society, Washington, D.C., 1994; Abstract ORGN 319.

(2) Elderfield, R. C.; Gilman, R. E. *Phytochemistry* **1972**, *11*, 339.

(3) Nordman, C. E.; Nakatsu, K. *J. Am. Chem. Soc.* **1963**, *85*, 353.

(4) Garnick, R. L.; Le Quesne, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4213.

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(6) Rahman, A.; Silva, W. S. J.; Alvi, K. A.; De Silva, K. T. D. *Phytochemistry* **1987**, *26*, 865.

(7) Rahman, A.; Qureshi, M. M.; Muzaffar, A.; De Silva, K. T. D. *Heterocycles* **1988**, *27*(3), 725.

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(9) The spirocyclic carbon in the nomenclature of the natural oxindole alstonisine **1** is designated C-7 while the spirocyclic carbon for the nomenclature of the parent 8-azabicyclic oxindole ring system **5** is designated C-6.

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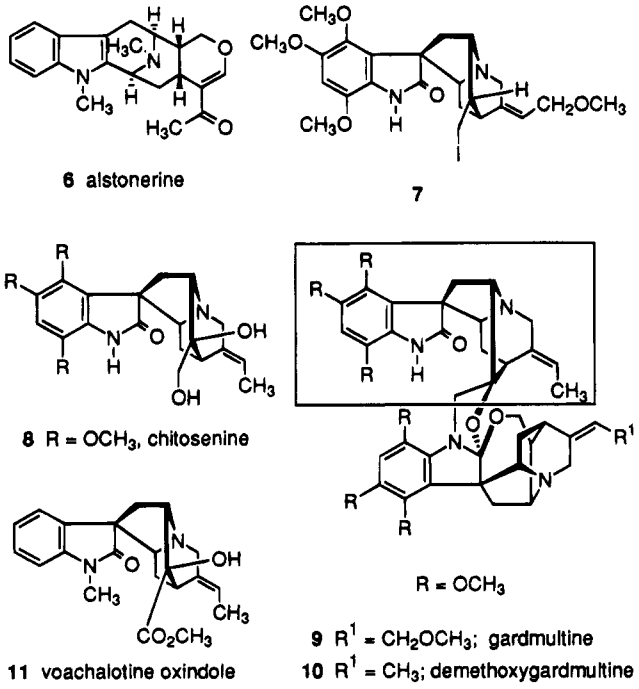
oxindole **7**, prepared from gardmultine,[11] in a formulation known to inhibit ulcers.[12] Interestingly, this alkaloid is diastereomeric at C(7) with respect to alstonisine (**1**).

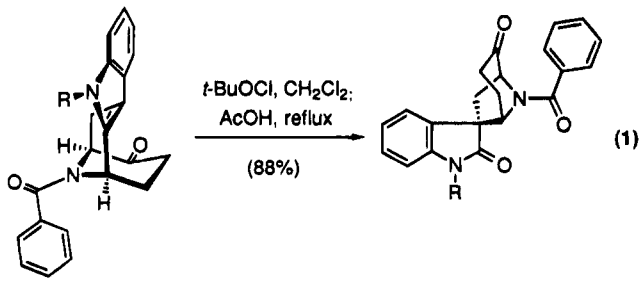
Chitosenine (**8**), a monomeric base isolated from *Gardneria multiflora* Makino,[13] also contains the substructure related to **5**; however, again the configuration of the spirocyclic carbon [C-7 in alstonisine (**1**)] in oxindole **8** is



opposite to that found in the *Alstonia* oxindoles **1**–**3**. Sakai and co-workers have established the configuration of the ethylidene function of this base by ^{13}C NMR spectroscopic experiments.[14] The *Gardneria* oxindole alkaloids exhibit short-lived inhibitory activity *in vivo* of ganglionic transmission in both rats and rabbits.[15] Two bisindoles, gardmultine (**9**) and desmethoxygardmultine (**10**), have also been isolated from *Gardneria multiflora*[16] and contain oxindole moieties related to chitosenine (**8**). The structure of gardmultine (**9**) was deduced by chemical and spectroscopic evidence[11,16] and concurrently established by single crystal X-ray analysis.[17] Braekman and co-workers previously isolated voachalotine oxindole (**11**) from *Voacanga chalotiana* Pierre ex Stapf which also contains the spiropyrrolidine ring system present in **5**.[18] The isolation of oxindoles **8**–**11** suggests that alkaloids which contain the substructure **5** may be more prevalent in plants than previously realized. This amplifies the interest for a stereochemically complementary entry into oxindoles related to **5** of either chirality at the spirocyclic carbon [C(6) in **5** and designated C(7) in **1**–**3**[9]].

Several approaches for the construction of spiroannelated indolines have been reported recently. The key spirocyclic centers have been constructed principally through anionic routes,[19] aryl radical cyclizations,[20,21] intramolecular Heck reactions,[22] and oxidations of indole double bonds.[23] The anionic routes developed by Fleming and co-workers are stereochemically complementary and stereoselective (>83% de).[19] Hart and Wu utilized a radical cyclization similar to the method of Jones[21a-c] to form the spirocenter in a stereoselective synthesis of the natural oxindole gelsemine.[21d] Overman and co-workers have described the palladium-catalyzed transformation of substituted anilines directly into spirocyclic oxindoles.[22a,b,d] When this latter procedure was conducted in the presence of (*R*)-(+)-BINAP, spirocyclic oxindoles were obtained with 66–71% ee.[22d] Moreover, this same group applied the intramolecular Heck cyclization sequence to construct the spirocenter of an intermediate required for the synthesis of gelsemine.[22e] A stereochemically complementary synthesis of this key intermediate by variation of the additive/solvent combination was also described. Recently, palladium-catalyzed cascade cyclizations to form spirooxindoles have also been developed.[22f] Güller and Borschberg have reported an interesting diastereoselective conversion of indolenines into oxindoles and pseudoindoxyls using a two-step approach with 3-chloroperoxybenzoic acid/trifluoroacetic acid in CH_2Cl_2.[23b] These authors later demonstrated that these pseudoindoxyls could be quantitatively converted into oxindoles stereoselectively by the action of BF_3–etherate in CH_2Cl_2.[23c]

Several years ago the diastereoselective conversion of the N_a-hydrogen analog (±)-5-methyl-9-oxo-6,7,8,9,10,-11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (**12a**) into spirocyclic oxindole **13a** via the chloroindolenine approach was reported (eq 1).[24] Unfortunately, this method



12a R = H **13a** R = H

12b R = CH_3 (no oxindole formed) **13b** R = CH_3 (not observed)

failed for conversion of the N_a-methyl-N_b-benzoyl derivative **12b** into the corresponding N_b-benzoyl oxindole **13b**. The N_a-alkyl analogs of structure **12a** will not readily undergo oxidation of the indole 2,3-double bond with *tert*-butyl hypochlorite; a step which must precede the rearrangement. Moreover, a method which would provide entry into either spirocyclic oxindole, diastereomeric at

(10) For reviews on *Alstonia* alkaloids, see: (a) Bi, Y.; Hamaker, L. K.; Cook, J. M. *Studies in Natural Products Chemistry*. In *Bioactive Natural Products;* Basha, F. Z., Rahman, A., Eds.; Elsevier Science: Amsterdam, 1993; Part A, Vol. 13, pp 383–432. (b) Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Sarpagine Alkaloids. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed; Pergamon: London, 1994; in press.

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(13) Aimi, N.; Yamaguchi, K.; Sakai, S.; Haginiwa, J.; Kuro, A. *Chem. Pharm. Bull.* **1978**, *26*, 3444.

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(20) (a) Yang, C.-C.; Chang, H.-T.; Fang, J.-M. *J. Org. Chem.* **1993**, *58*(11), 3100. (b) **Note:** The structure of alstonisine **1** was incorrectly represented in this paper. In addition, alstonisine **1** was incorrectly referred to as an *Aspidosperma* alkaloid.

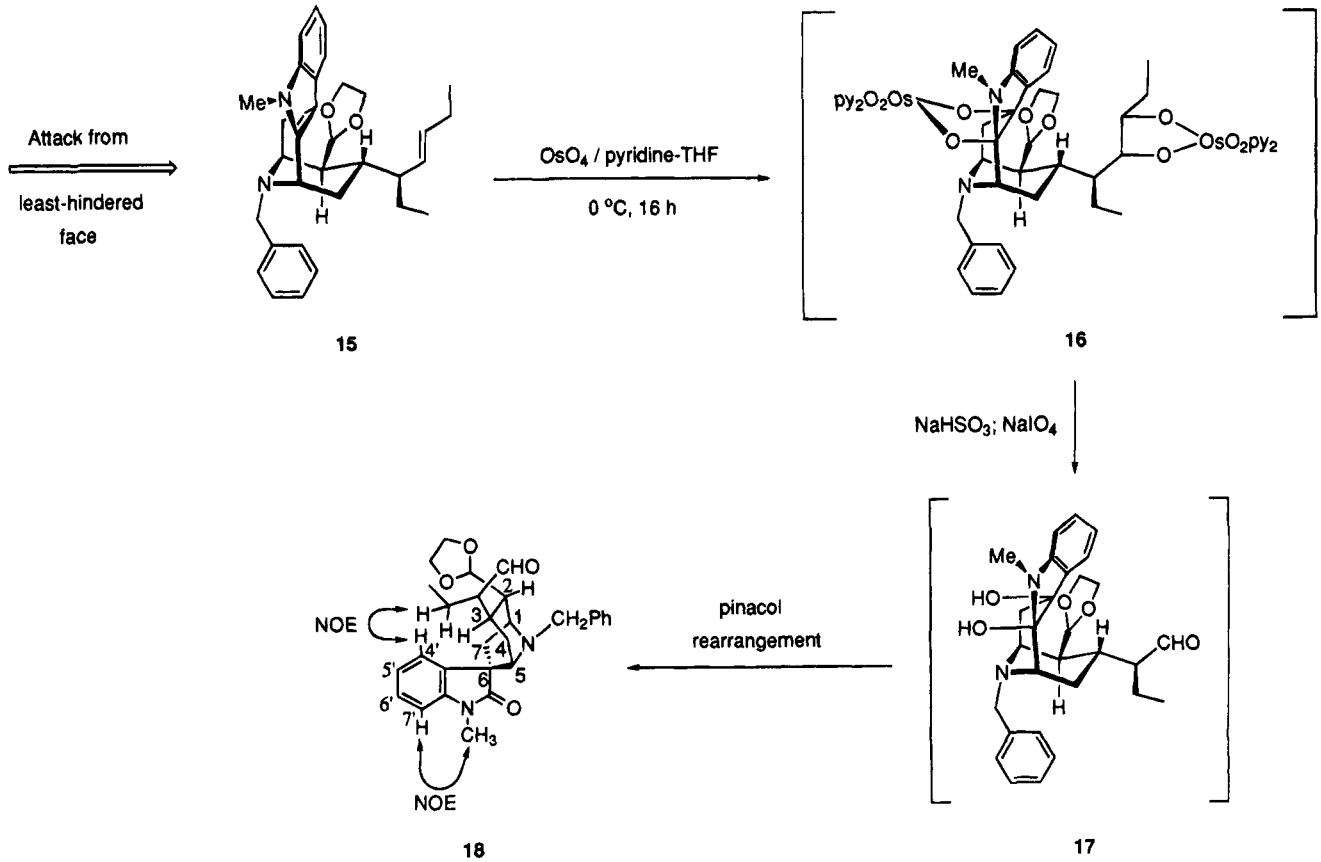
C-6 (see structure **5**[9]), would be particularly useful. Our recent results[1] in this area form the basis of this report.

In 1988 an enantiospecific synthesis of the (−)-N_b-benzyltetracyclic ketone **14a** was reported on a multigram scale,[25] and this material has been employed for the total synthesis of (−)-alstonerine (**6**),[26] (−)-suaveoline,[27] and (+)-macroline,[28] as well as the ajmaline-related alkaloids (−)-raumacline and (−)-N_b-methylraumacline.[27] The ability to prepare this (−)-N_a-methyl-N_b-benzyl ketone **14a** on a multigram scale has prompted a new approach to the conversion of the (−)-N_a-methyl-N_b-benzyltetracyclic ketone **14a** into the desired oxindole **21a** with the same configuration[9] at the spirojuncture [C(7)] present in alstonisine (**1**). Earlier, during the synthesis of (−)-raumacline,[27] the synthetic N_b-benzyl tetracyclic monoketal **15** was stirred with osmium tetraoxide in pyridine, and this was followed by periodate oxidation to provide oxindole **18** as an unwanted byproduct. Esmond and Le Quesne had also observed a similar formation of an oxindole during dihydroxylation of a key intermediate with OsO_4/pyridine in their biomimetic synthesis of macroline.[29] A proposed pathway for the transformation of monoketal **15** to oxindole **18** is outlined in Scheme 1. This conversion occurred with complete diastereoselectivity to furnish oxindole **18** with the correct configuration[9] relative to alstonisine (**1**). The configuration at the spiro center was established by NOE-difference spectroscopy. All of the signals in the ^1H NMR spectrum of oxindole **18** were assigned with the aid of a COSY experiment (see Experimental Section, Table 2). The aromatic proton H-7′ was assigned from the NOE enhancement observed in the proton spectrum of oxindole **18** when the N_a-methyl protons were irradiated. This result permitted the assignment of H-4′ via the COSY spectrum. A NOE enhancement in the proton spectrum of oxindole **18** was also observed between the CH_2 protons of the ethyl group and H-4′ which would not have been observed in the other diastereomer. Analysis of interactions by molecular models suggests that attack of the osmium reagent[30] on the indole 2,3-double bond has occurred from the less hindered convex face of the indole 2,3-double bond to furnish an intermediate bisosmate ester **16**. It is believed that the apically positioned acetal group effectively blocked the concave face of the double bond to attack by the OsO_4/pyridine reagent. Upon conversion ($NaIO_4$) of the intermediate **16** into the diol–aldehyde[31] **17** and subsequent pinacol rearrangement[32] oxindole **18** was obtained. In agreement with this result, Sakai and co-workers had earlier utilized the osmium tetraoxide/pyridine reagent to prepare oxindoles of the *Gelsemium* alkaloids from their corresponding indoles.[33] This method appears to occur with complete diastereoselectivity to provide the oxindole with the natural configuration about the spiro juncture in the gelsemium-type bases. In the present study, the conversion of N_a-methyltetracyclic analogs into their corresponding oxindoles with a high degree of diastereoselectivity is described in cases which the substrates are devoid of a group other than hydrogen situated either at the equatorial position at C-16 or the axial position at C-15 to direct the stereoselectivity.

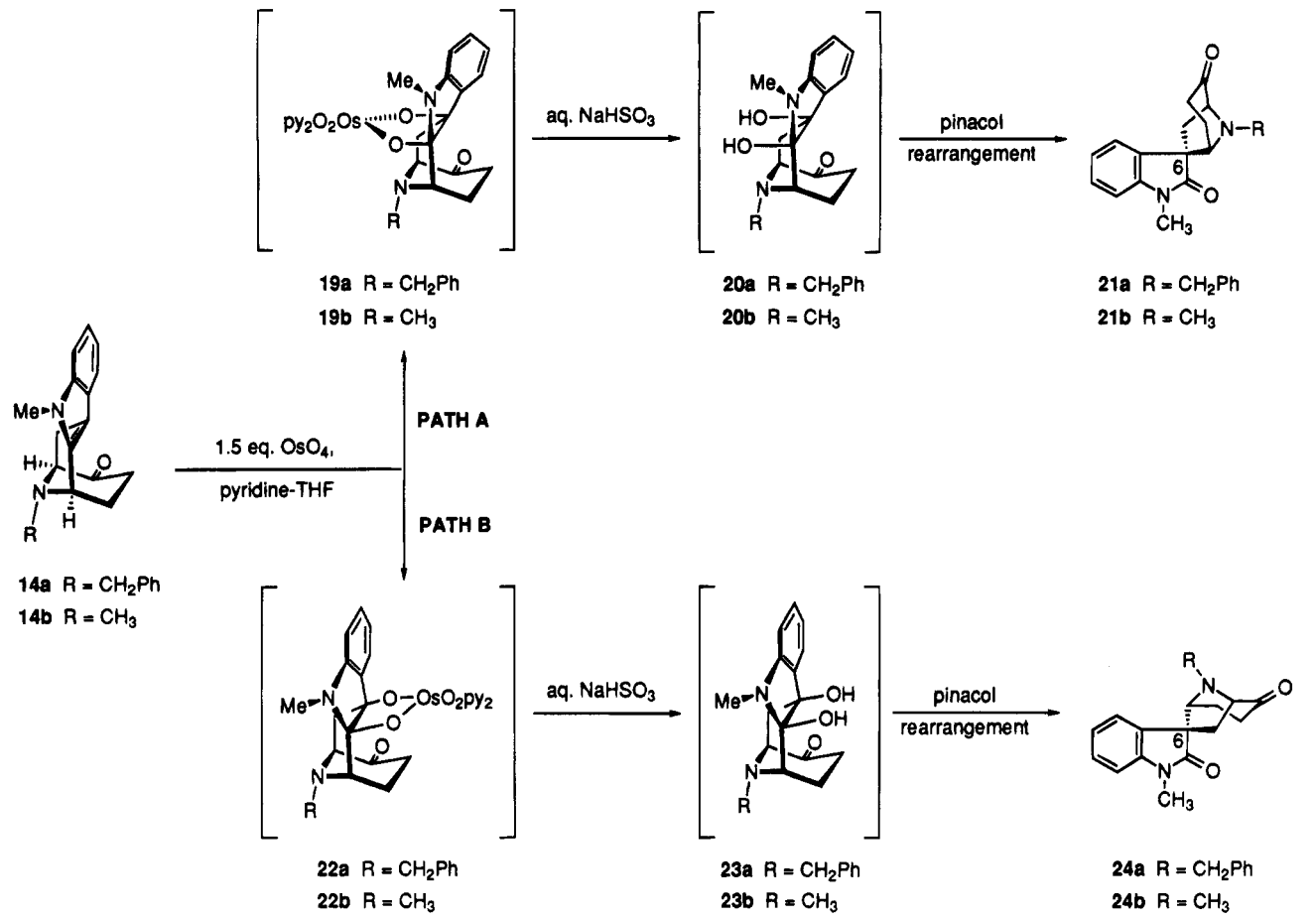
Results and Discussion

Racemic N_b-benzyltetracyclic ketone **14a** was treated with osmium tetraoxide in the presence or absence of tertiary amines (Schemes 2 and 3; Table 1). When a solution of racemic or (−)-ketone **14a** in THF–pyridine (2:1) was stirred with a solution of osmium tetraoxide (1.5 equiv) in THF–pyridine (2:1) at room temperature,

Scheme 1



Scheme 2

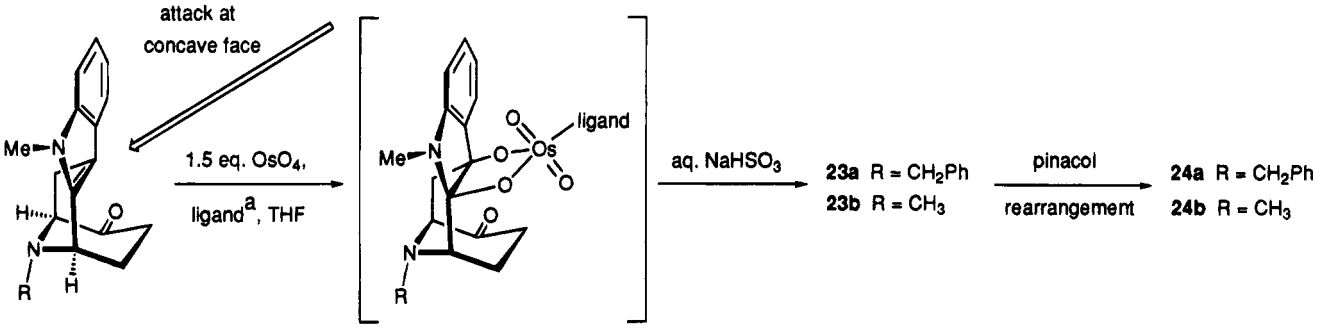


19a R = CH_2Ph **19b** R = CH_3 **20a** R = CH_2Ph **20b** R = CH_3 **21a** R = CH_2Ph **21b** R = CH_3

14a R = CH_2Ph **14b** R = CH_3

22a R = CH_2Ph **22b** R = CH_3 **23a** R = CH_2Ph **23b** R = CH_3 **24a** R = CH_2Ph **24b** R = CH_3

Scheme 3



14a R = CH_2Ph **14b** R = CH_3 **27a** R = CH_2Ph **27b** R = CH_3 **23a** R = CH_2Ph **23b** R = CH_3 **24a** R = CH_2Ph **24b** R = CH_3

[a] ligand = quinuclidine, DHQ-CLB, DHQD-CLB, $(DHQ)_2PHAL$, $(DHQD)_2PHAL$

followed by reductive workup with *aqueous* $NaHSO_3$ and flash chromatography, the oxindoles **21a** and **24a** were produced in a 1:1 ratio in 36% yield (Scheme 2; Table 1, entries 3 and 10). Presumably, osmium tetraoxide forms a reversible complex which incorporates the pyridine ligand.[34] The indole 2,3-double bond of the ketone **14a** is initially attacked by the OsO_4–pyridine complex and then a pyridine coordinates to the osmium metal center to subsequently produce intermediates **19a** and **22a**.[35] Alternatively, initial attack of the indole 2,3-double bond on the osmium metal center to form an osmium–carbon bond may occur to furnish osmaoxetane intermediates

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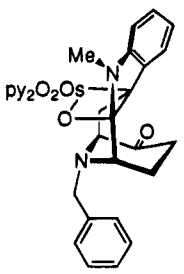
Table 1. Results from the Treatment of Ketones 12b, 14a, and 14b with Osmium Reagents[a]

entry	ketone	ligand[b]	equiv of OsO_4	temp, °C	time (d)	oxindole	yield, %	**21**:**24**[c]
1	(±)-**14a**		1.0	reflux	3	(±)-**21a/24a**	44	91:9
2	(±)-**14a**		3.0	reflux	3	(±)-**21a/24a**	32	50:50
3	(±)-**14a**	pyridine	1.5	rt	3	(±)-**21a/24a**	36	50:50
4	(±)-**14a**	quinuclidine	1.5	rt	3	(±)-**21a/24a**	11	25:75
5	(±)-**14a**	DHQ−CLB	1.5	rt	3	(±)-**21a/24a**	82	24:76
6	(±)-**14a**	DHQD−CLB	1.5	rt	3	(±)-**21a/24a**	76	48:52
7	(±)-**14a**	$(DHQ)_2PHAL$	1.5	rt	3	(±)-**21a/24a**	76	20:80
8	(±)-**14a**	$(DHQD)_2PHAL$	1.5	rt	3	(±)-**21a/24a**	66	47:53
9	(−)-**14a**		1.0	reflux	3	**21a/24a**	42	91:9
10	(±)-**14a**	pyridine	1.5	rt	3	**21a/24a**	36	50:50
11	(−)-**14a**	DHQ−CLB	1.5	rt	3	**21a/24a**	91	3:97
12	(−)-**14a**	DHQD−CLB	1.5	rt	3	**21a/24a**	77	20:80
13	(−)-**14a**	$(DHQ)_2PHAL$	1.5	rt	3	**21a/24a**	81	25:75
14	(−)-**14a**	$(DHQD)_2PHAL$	1.5	rt	3	**21a/24a**	82	20:80
15	(±)-**12b**		1.0	rt	3	(±)-**13b**	0	
16	(±)-**14b**		1.0	reflux	3	(±)-**24b**	36	0:100
17	(±)-**14b**	pyridine	1.5	rt	3	(±)-**24b**	40	0:100
18	(±)-**14b**	DHQ−CLB	1.5	rt	3	(±)-**24b**	66	0:100

[a] Reactions conducted in THF under a nitrogen atmosphere. [b] Ligands: DHQ−CLB = dihydroquinine 4-chlorobenzoate; DHQD−CLB = dihydroquinidine 4-chlorobenzoate; $(DHQ)_2PHAL$ = dihydroquinine 1,4-phthalazinediyl diether; $(DHQD)_2PHAL$ = dihydroquinidine 1,4-phthalazinediyl diether. [c] Ratios of diastereomers were obtained by ^1H NMR spectroscopy using a pulse delay of 15 s. The diastereomeric ratios of the mixtures of N_b-benzyloxindoles **21a**:**24a** were determined by ^1H NMR spectroscopy (500 MHz, $CDCl_3$) on the purified mixture (flash chromatography) by integration of the N_a-methyl singlets (δ 3.23 for **24a** and δ 3.19 for **21a**) and confirmed by integration of the H-7α protons (δ 2.54 for **24a** and δ 2.91 for **21a**). For most reactions the diastereomeric ratios were also determined on the crude product mixtures. No significant differences in the **21a**:**24a** ratio were observed between crude and purified mixtures.

25 and **26**.[36] These initially formed osmaoxetanes **25** and



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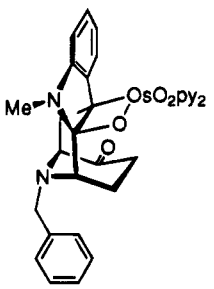

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26 would be expected to rearrange to osmate esters **19a** and **22a**. Osmate esters, similar to **19a** and **22a**, have been isolated and characterized previously.[37] The osmate esters **19a** and **22a** were then hydrolyzed with *aqueous* sodium bisulfite to give the corresponding *cis*-diols **20a** and **23a**, respectively, which subsequently underwent a pinacol rearrangement with 2,3-bond migration. The displacement took place on the protonated 3-hydroxyl function from the back side to give the resultant oxindoles **21a** and **24a**, respectively. The relatively small size of the initial OsO_4−py complex[34] did not permit discrimination between attack on the diastereomeric faces of the indole 2,3-double bond of substrate **14a**. When a solution of ketone **14a** in THF was treated with a mixture of osmium tetraoxide and quinuclidine[38] in THF, however, a 3:1 ratio of diastereomeric oxindoles **24a**:**21a** was produced (Table 1, entry 4). This latter case demonstrated that an increase in size of the amine ligand favored initial reaction of the osmium reagent at the concave face of ketone **14a**. The structure of an osmium complex which incorporates one molecule of quinuclidine has been reported.[38] Sharpless and co-workers have elegantly demonstrated that reactions involving the treatment of achiral olefins with osmium tetraoxide in the presence of functionalized dihydroquinine and dihydroquinidine ligands are stereochemically complementary[39] and that the dihydroquinine and dihydroquinidine ligands complex with osmium through the quinuclidine nitrogen.[40] Since derivatives of these *Cinchona* alkaloids are commercially available, the effect of these ligands on the stereochemical outcome of the conversion of 8-azabicyclo[3.3.1]indole **14a** into the corresponding ox-

(24) Hollinshead, S. P.; Grubisha, D. S.; Bennett, D. W.; Cook, J. M. *Heterocycles* **1989**, *29*(3), 529.

(25) Zhang, L.-H.; Bi, Y.-Z.; Yu, F.-X.; Menzia, G.; Cook, J. M. *Heterocycles* **1992**, *34*(3), 517.

(26) Zhang, L. H.; Cook, J. M. *J. Am. Chem. Soc.* **1990**, *112*(10), 4088.

(27) (a) Fu, X.; Cook, J. M. *J. Am. Chem. Soc.* **1992**, *114*(17), 6910. (b) Fu, X.; Cook, J. M. *J. Org. Chem.* **1993**, *58*(3), 661.

(28) Bi, Y.; Cook, J. M. *Tetrahedron Lett.* **1993**, *34*(28), 4501.

(29) Esmond, R. W.; Le Quesne, P. W. *J. Am. Chem. Soc.* **1980**, *102*, 7116.

(30) For a review on osmium tetraoxide/amine reagents in the formation of *cis*-diols from olefins, see: Schröder, M. *Chem. Rev.* **1980**, *80*, 187 and references cited therein.

(31) The conversion of indoles to indoline glycols, such as **20a** and **23a**, upon treatment with osmium tetraoxide, followed by hydrolysis, has been known for over 40 years: (a) Witkop, B. *J. Am. Chem. Soc.* **1950**, *72*, 614. (b) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 2188.

(32) (a) For a review of rearrangements of indoline glycols, see: Giovanni, V. E.; Karrer, F. *Chimia* **1967**, *21*, 517. (b) The stereochemical outcome of the pinacol rearrangement with respect to the migration terminus is influenced by the same factors which control the stereochemical outcome in Wagner−Meerwein rearrangements. Migrations (1,2-shifts) in rigid, polycyclic systems are effective only if the torsional angle between the migrating group and the vacant carbocation orbital are less than approximately 30°; see: Saunders, M.; Chandrasekhar, J.; Schleyer, P. v. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed; Academic: New York, 1980; p 27. Nickon, A.; Weglin, R. C. *J. Am. Chem. Soc.* **1975**, *97*(5), 1271. In the pinacol rearrangements of the tetracyclic indole systems investigated in this study, the migrating group can only rearrange effectively to the terminal carbon atom from the side opposite the hydroxyl leaving group due to these torsional angle constraints.

(33) (a) Sakai, S.; Aimi, N.; Yamaguchi, K.; Yamanaka, E.; Haginiwa, J. *Tetrahedron Lett.* **1975**, (10), 719. (b) Sakai, S.; Aimi, N.; Yamaguchi, K.; Yamanaka, E.; Haginiwa, J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1257.

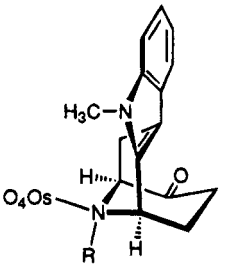
(34) (a) Criegee, R.; Marchand, B.; Wannowius, H. *Liebigs Ann. Chem.* **1942**, *550*, 99. (b) Griffith, W. P.; Rossetti, R. *J. Chem. Soc., Dalton Trans.* **1972**, 1449.

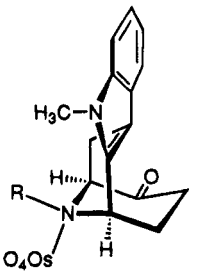
(35) (a) Criegee, R. *Angew. Chem.* **1938**, *51*, 519. (b) Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Bioinorg. Chem.* **1971**, *1*, 35. (c) Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Inorg. Chem.* **1972**, *11*, 2621. (d) Collin, R. J.; Jones, J.; Griffith, W. P. *J. Chem. Soc., Dalton Trans.* **1974**, 1094. (e) Rosa, J. J.; Sigler, P. B. *Biochemistry* **1974**, *13*(25), 5102. (f) Daniel, F. B.; Behrman, E. J. *J. Am. Chem. Soc.* **1975**, *97*(25), 7352. (g) Clarke, R. L.; Behrman, E. J. *Inorg. Chem.* **1975**, *14*, 1425. (h) Chang, C.-H.; Beer, M.; Marzilli, L. G. *Biochemistry* **1977**, *16*(1), 33. (i) Ragazzo, J. A.; Behrman, E. J. *Bioinorg. Chem.* **1976**, *5*, 343. (j) Jorgensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, *108*, 1867.

indoles was immediately investigated (Scheme 3). Entries 4–8 and 11–14 in Table 1 reflect that the production of oxindole **24a** was favored in every case in which a bulky tertiary quinuclidine ligand was used. Indeed, when dihydroquinine 4-chlorobenzoate was employed as the exogenous amino ligand (Table 1, entry 11), ketone (−)-**14a** was converted into oxindole **24a** with 30:1 diastereoselectivity in 91% isolated yield. In all of these cases attack of the osmium reagent (OsO_4/*Cinchona* derivative) occurred preferentially from the concave face of the indole 2,3-double bond of substrate **14a** to provide osmate ester **27a**. Upon hydrolysis (aqueous $NaHSO_3$) of osmate ester **27a** and subsequent pinacol rearrangement, oxindole **24a** was produced. Furthermore, attack of the osmium reagents which contain bulky amino ligands on the 2,3-double bond occurred preferentially from the concave face without regard to asymmetry in the pendent ligand. When the reaction sequence was conducted in the presence of the bulky Sharpless phthalazine ligands,[42] $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$, the facial discrimination was reduced. As anticipated, some match of configurations between the *Cinchona* derivative and the substrate was necessary to optimize the diastereoselectivity.

A difference in diastereoselectivity was noted when racemic ketone (±)-**14a** versus optically active ketone (−)-**14a** was employed as the substrate for conversion into oxindoles (±)-**21a/24a** and optically active **21a/24a,** respectively, using osmium tetraoxide and these same *Cinchona* derivatives (Table 1, entries 5–8 versus 11–14). Almost complete diastereoselectivity (94% de) was observed in 91% isolated yield when the key ketone (−)-**14a** was treated with OsO_4/dihydroquinine 4-chlorobenzoate (Table 1, entry 11). On the other hand, treatment of racemic ketone (±)-**14a** with OsO_4/dihydroquinine 4-chlorobenzoate produced oxindole (±)-**24a** in only 52% de (Table 1, entry 5). Higher diastereoselectivity was generally observed in the conversion of optically active ketone (−)-**14a** into oxindole **24a** in all cases except when $OsO_4/(DHQ)_2PHAL$ was utilized. In this latter case, little difference in the diastereoselectivity was observed regardless of whether racemic or (−)-ketone **14a** served as the substrate [4:1 diastereoselectivity from (±)-**14a** vs 3:1 from (−)-**14a**; Table 1, entries 7 and 13]. Clearly, the asymmetry present in the ketone substrate is sensitive to the asymmetry present in the osmium reagent.[43]

Drawing upon the knowledge gained during previous alkaloid syntheses in this laboratory, it was believed that use could be made of the proximity of the piperidine nitrogen atom to the convex face of the indole 2,3-double bond. In earlier work, for example, the complexation of 9-BBN to the piperidine nitrogen of a macroline-related substrate blocked one face of a double bond to allow stereoselective hydroboration.[26] In the present case, it was felt that osmium tetraoxide would first coordinate to the piperidine nitrogen atom, and then the osmylation would occur from the convex face of the substrate intramolecularly. Indeed, when either racemic or (−)-tetracyclic ketone **14a** was treated with 1 equiv of osmium tetraoxide in the absence of tertiary amines, oxindole **21a** was produced in 82% de (10:1) in 42–44% yield (Table 1, entries 1 and 9). The asymmetry present in the substrate **14a** had no effect upon the diastereoselectivity. It appears that osmium tetraoxide first complexes with the piperidine nitrogen atom of ketone **14a** at 0 °C to furnish complex **28a**. This complexation is

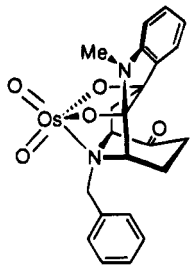




28a R = CH_2Ph **29a** R = CH_2Ph

28b R = CH_3 **29b** R = CH_3

presumably favored due to the axial preference (with respect to ring D) of the benzyl group. Single crystal X-ray analysis of a N_b-benzyltetracylic derivative indicated that the benzyl group rested in the axial position of the D ring in the crystal.[44] The concomitant complexation of osmium at the equatorial position (with respect to ring D) facilitated intramolecular attack of the osmium reagent to furnish osmate ester **30** upon heating at reflux.



30

If complexation occurred at the axial position (with respect to the D ring) to give complex **29a**, intramolecular delivery of the osmium reagent to the indole 2,3-double bond would be unlikely. The osmate ester **30** was then reduced by sodium bisulfite, and the *cis*-diol **20a** which resulted underwent a pinacol rearrangement to furnish oxindole **21a** with 10:1 overall diastereoselectivity. The configuration[9] about the spirocyclic carbon-6 in oxindole **21a** was found to be the same as in alstonisine (**1**) [C(7)] by NMR spectroscopic experiments. Since 9% of the diastereomeric spirocyclic oxindole **24a** was formed in this reaction sequence, either attack of osmium tetraox-

(36) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.

(37) (a) Cleare, M. J.; Hydes, P. C.; Griffith, W. P.; Wright, M. J. *J. Chem. Soc., Dalton Trans.* **1977**, 941. (b) Cartwright, B. A.; Griffith, W. P.; Schröder, M.; Skapski, A. C. *J. Chem. Soc., Chem. Commun.* **1978**, 853. (c) Schröder, M.; Nielson, A. J.; Griffith, W. P. *J. Chem. Soc., Dalton Trans.* **1979**, 1607.

(38) Griffith, W. P.; Skapski, A. C.; Woode, K. A.; Wright, M. J. *Inorg. Chim. Acta* **1978**, *31*, L413.

(39) (a) Ogino, Y.; Chen, H.; Manoury, E.; Shibata, T.; Beller, M.; Lübben, D.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 5761. (b) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

(40) Svendsen, J. S.; Markó, I.; Jacobsen, E. N.; Rao, C. P.; Bott, S.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2263.

(41) The small amount of oxindole **21a** which was produced in this sequence could have arisen from competitive attack at the convex face of the 2,3-double bond by OsO_4 or by OsO_4 complexes such as **28a** and **29a**. However, prior mixing should have converted all of the free osmium tetraoxide into the complex of the OsO_4/*Cinchona* derivative. Therefore, it seems likely that the initial attack of the complex of the OsO_4/*Cinchona* derivative is not completely stereoselective, and the 3% of the diastereomeric oxindole **21a** was produced from attack of the osmium reagent at the convex face. Since the complexation of OsO_4 to the amino ligands is reversible (reference 34), the formation of complexes **28a** and **29a** is reasonable.

(42) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

ide[45] at the indole 2,3-double bond competes, albeit ineffectively, with complexation or the initially formed complexes **28a** and **29a** serve as sterically demanding reagents. These complexes **28a** and **29a** would provide preferential attack on the concave face of the indole 2,3-double bond to subsequently provide a small amount of the diastereomeric oxindole **24a**. The amount of ketone **14a** that was neither converted into oxindoles **21a** and **24a** nor recovered was presumably oxidized to *N*-oxides.[46] When the ketone **14a** was treated with a large excess of osmium tetraoxide (3 equiv), a 1:1 ratio of oxindoles **21a** and **24a** was produced in somewhat lower yield (32%). This result suggests that the osmium tetraoxide is indeed initially complexed to the piperidine nitrogen atom. However, attack of noncomplexed OsO_4 at the concave face of the indole 2,3-double bond may compete with intramolecular delivery of the complexed OsO_4. In this latter case a higher percentage of ketone substrate **14a** was converted via intermolecular processes into oxindole **24a**. In addition, the excess OsO_4 was available to oxidize the substrate (another intermolecular process). The use of only 1 equiv of osmium tetraoxide and a 1 h precomplexation period at O °C is essential to maximize the diastereoselective conversion of ketone **14a** into oxindole **21a**. Any alteration of this procedure will produce a higher percentage of oxindole **24a**.

Further evidence for the advent of the complexation/intramolecular delivery of osmium tetraoxide in the previous example (1 equiv of OsO_4) was obtained by treatment of N_b-benzoyl ketone **12b** with osmium tetraoxide in THF. Amides have been shown neither to complex osmium nor to direct the osmylation.[47] This process failed to convert the N_b-benzoyl ketone **12b** into N_b-benzoyloxindole **13b** or its diastereomer. Only the starting ketone **12b** was recovered (95% recovery) from this sequence. Clearly, the benzoyl group of substrate **12b** is approximately the same size as the benzyl group in ketone **14a**. However, the lone pair of electrons of the piperidine nitrogen is delocalized into the carbonyl of the amide function and not readily available to coordinate with osmium tetraoxide. This example demonstrates that neither the complexation of OsO_4 (and subsequent intramolecular oxidation of the indole 2,3-double bond) occurs nor uncomplexed OsO_4 reacts with substrate **12b** even from the concave face of the indole 2,3-double bond at room temperature. In these systems evidently the OsO_4 is not reactive enough at room temperature to oxidize the indole double bond without previous ligation to a nitrogen function.

When N_b-methyl ketone **14b** was treated with osmium tetraoxide, osmium tetraoxide/pyridine, or osmium tetraoxide/dihydroquinine 4-chlorobenzoate, only one diastereomer, N_b-methyloxindole **24b**, was produced in 36–66% yields (Schemes 2 and 3, Table 1, entries 16–18). The smaller N_b-methyl substituent in **14b** and other macroline-related indoles is believed to preferentially occupy the equatorial position of the D ring.[48] As a result, the ligation and subsequent attack of osmium reagent would be hindered by the N_b-methyl substituent and only osmate ester **22b** (or **27b** in the case of OsO_4/DHQ-CLB or **29b** in the case of OsO_4 alone) and subsequently diol **23b** were formed irregardless of the osmium reagent. Diol **23b** underwent a pinacol rearrangement to furnish spirocyclic oxindole **24b** with complete diastereoselectivity. The chirality at C(6) of N_b-methyloxindole **24b** is identical to that of the spirocyclic carbons present in chitosenine **8** and voachalotine oxindole **11**.

NMR Spectroscopy

Identification of compounds **21a**, **24a**, and **24b** as oxindoles was made through ^{13}C NMR spectroscopy. Examination of the ^{13}C NMR spectra of these oxindoles indicates the presence of an amide resonance at δ 177–181, whereas the ^{13}C NMR resonance for the benzyl ketone carbonyl carbon of spiropseudoindoxyls in a similar system was found to be at 202.3 ppm.[23b] The ^{13}C NMR chemical shift difference of the newly formed carbonyl group of the oxindoles prepared in this investigation and the expected shift for the carbonyl of a pseudoindoxyl precludes the latter structure for these compounds.

The complete proton and carbon assignments for oxindoles **21a**, **24a**, and **24b** were relatively straightforward and were made with the combined results of the following experiments at 500 MHz: ^1H NMR spectroscopy, ^1H NMR spectroscopy (NOE-difference), ^{13}C NMR spectroscopy with broadband proton decoupling, DEPT, $^1H-^{13}C$ NMR correlation (HMQC), and COSY.

The following description of the complete proton and partial carbon assignments for oxindole **24a** serves as an example. The ^1H NMR signal assignments for the indole

(43) A reviewer has suggested the possibility that all of the reactions may pass through intermediates, such as **28a** and **29b**. The coordinated osmium tetraoxide moiety would then effectively block the convex face toward intermolecular attack of any osmium reagent. It is felt that this pathway is unlikely since prior mixing of OsO_4 in the presence of excess ligand should have bound the OsO_4 as the OsO_4/ligand complex. In addition, should this alternative pathway be operative, it is felt that reactions of **14a** with OsO_4/ligand complexes would give exclusively the oxindole **24a** formed by attack at the concave face as is observed in the reaction of N_b-methyl ketone **14b** with any osmium reagent which gave only oxindole **24b**. It is also believed that significant decomposition of complexes such as **28a** and **29a** would occur to give *N*-oxides as is suggested by the low yields obtained when ketone **14a** is treated with OsO_4 in the absence of exogenous aminoligands. Clearly, the 66–91% yields (with the bulk of the remainder recovered ketone **14a**) obtained when ketone **14a** is treated with OsO_4/*Cinchona* ligand complexes suggests that little decomposition occurs in these reactions.

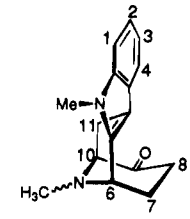
(44) Zhang, L.-H.; Trudell, M. L.; Hollinshead, S. P.; Cook, J. M. *J. Am. Chem. Soc.* **1989**, *111*(21), 8263.

(45) No reaction was observed between the N_b-benzoyl ketone **12b** in which the N_b-amide function resists complexation with osmium tetraoxide. This suggests that the complexation of OsO_4 with ketone **14a** occurs prior to the inter- or intramolecular cis-dihydroxylation.

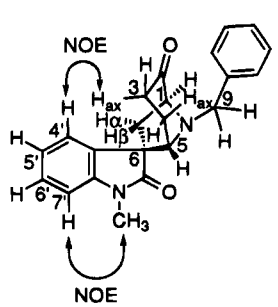
(46) Misra, R. K.; Saxena, S.; Singh, A. K. *Vijnana Parishad Anusandhan Patrika* **1989**, *31*, 83.

(47) Backenstrass, F.; Streith, J.; Tschamber, T. *Tetrahedron Lett.* **1990**, *31*(15), 2139.

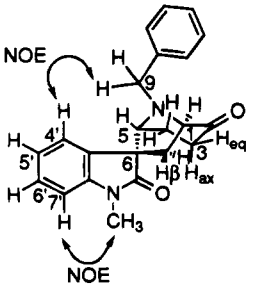
(48) (a) The N_b-methyl function of the macroline portion of the bisindole villastonine in the crystal has been shown to occupy the equatorial position of the D-ring and lies over the indole: Nordman, C. E.; Kumra, S. K. *J. Am. Chem. Soc.* **1965**, *87*(9), 2059. In addition, molecular mechanics calculations (Macromodel with MM2 force field parameters) indicate that the conformer of ketone **14b** with the N_b-methyl group in the equatorial position is more stable (by 1.8 kcalmol^{-1}) than the conformer with the N_b-methyl group in the axial position. The NOE data of the N_b-methyltetracyclic ketone **14b** also indicate that the N_b-methyl group preferentially occupies the equatorial position. When the signal at δ 2.45 (N_b-Me) was presaturated (500 MHz, $CDCl_3$), enhancements were observed in the following protons: H-6 (6.8%), H-10 (8.7%), and H-11a (4.6%). (b) Another possibility is that the complexes **28b** and **29b** attack the convex face of the OsO_4/**14b** complexes **28b** and **29b** or free ketone **14b** stereospecifically. This intermolecular process may be much faster than the intramolecular oxidation of the indole 2,3-double bond in the N_b-methyl series relative to the N_b-benzyl series.



benzene ring were made first by irradiation of the N_a-methyl singlet (δ 3.23) which produced an 18.3% NOE enhancement of the doublet at 6.81 ppm (H-7′). This was confirmed by irradiation of the doublet at 6.81 ppm which produced a 7.5% NOE enhancement of the N_a-methyl protons at 3.23 ppm. The remainder of the indole aromatic protons, H-6′ (triplet at δ 7.28), H-5′ (triplet at δ 7.12), and H-4′ (doublet at 7.85 ppm), were then assigned in a straightforward manner via the sequential correlations observed from the COSY spectra. The aliphatic portion of the molecule (8-azabicyclo[3.2.1]-octane ring system) contains two nonequivalent spin systems. Each spin system was readily identified from the COSY experiment. The methylene protons were identified from the HMQC spectrum after the carbon multiplicities were determined with the DEPT sequence. Proton H-5 (δ 3.16) was correlated via the COSY experiment to the multiplet at δ 2.29 (H-4_{ax}). The torsional angle of approximately 90° (minimum of the vicinal Karplus curve) between H-5 and H-4_{eq} precludes any strong coupling and, hence, any observable correlation between these nuclei in this COSY experiment. The geminal protons H-4_{ax} and the doublet of doublets at δ 2.21 (J = 14.5 and 9.7 Hz, H-4_{eq}) showed a strong correlation in the COSY spectrum, as expected. Proton H-4_{ax} was also coupled to the resonance at δ 3.55 (H-3_{ax}) which appears as a doublet of triplets (J = 17.5, 9.7, 9.7 Hz). Proton H-3_{ax} is found downfield due to its proximity to the amide carbonyl function. No correlation was expected or observed between H-4_{eq} and H-3_{ax} due to the approximate 90° torsional angle which relates these atoms. The proton (H-3_{eq}) at δ 2.44 (dd, 17.5, 8.6 Hz) was strongly correlated to both H-3_{ax} and H-4_{ax} in the COSY spectrum. The other aliphatic methine proton, H-1, at δ 3.70 (br d, J = 7.3 Hz) was coupled to both H-7α (δ 2.54, dd, J = 13.7, 7.3 Hz) and H-7β at δ 2.42 (dd, J = 13.7, 0.7 Hz), because these protons are bonded to a five-membered ring. The protons attached to carbon-7 were strongly correlated in the COSY spectrum. All of the geminal proton pairs were readily identified through the HMQC spectrum and their geminal coupling constants ($^2J_{H-H}$ = 13−15 Hz). To establish the configuration of oxindole **24a**, H-4′ was irradiated, and only small NOE enhancements at the benzyl methylene protons (H-9) were observed. In addition, the irradiation of H-3_{ax} did not produce any enhancement of the H-4′ signal. This result firmly established the configuration of oxindole **24a** as shown. The structural and chemical shift assignments for diastereomer **21a** and the N_a,N_b-dimethyloxindole **24b** were made in a similar fashion. The ^{13}C NMR signals which contain multiplicity were then assigned through the ^{1}H−^{13}C NMR correlation experiment (HMQC).



21a



24a

The configuration of oxindole **21a** was established based upon the presence of NOE enhancements between H-4′ and H-3_{ax} in the NOE-difference spectrum. The distance between the van der Waals radii of protons H-4′ and H-3_{ax} for diastereomer **21a** was on the order of 2.1 Å as determined by calculations using Macromodel with MM2 force field parameters, and an NOE correlation is expected. For diastereomer **21a**, which contains the same configuration about the spirocyclic carbon[9] (C-6) as alstonisine (**1**), an NOE enhancement was observed at H-3_{ax} (6.3%), H-4_{eq} (4.0%), and H-7α (δ 2.91, 1.3%) upon irradiation of the aromatic proton H-4′. In addition, irradiation of H-3_{ax} produced an 11.8% enhancement of H-4′ in the NOE difference spectrum. This result is consistent with the report by Rahman and co-workers who have previously described the determination of the configuration of 16-hydroxy-N_b-demethylalstophylline oxindole (**3**) by NMR spectroscopic methods which included NOE experiments.[7]

The diastereomeric ratios of the mixtures of N_b-benzyloxindoles **21a**−**24a** were determined by ^{1}H NMR spectroscopy (500 MHz, $CDCl_3$, 15 s pulse delay) on the purified mixture (flash chromatography) by integration of the N_a-methyl singlets (δ 3.23 for **24a** and δ 3.19 for **21a**) and confirmed by integration of H-7α protons (δ 2.54 for **24a** and δ 2.91 for **21a**). For most reactions the diastereomeric ratios were also determined on the crude product mixtures. In these cases, no significant differences in the **21a**:**24a** ratio was observed between the crude and purified mixtures.

Summary

Examination of the results of this study demonstrates that oxindole **21a** which is related to alstonisine **1** can be prepared with a 10:1 diastereoselectivity from the N_b-benzyltetracyclic ketone **14a** by an intramolecular OsO_4 complexation−control mechanism. To our knowledge no previous examples are known in which stereoselective osmylation of the 2,3-double bond of indole alkaloids has been reported to take place in an intramolecular fashion. However, stereoselective intramolecular osmylations have been demonstrated for acyclic olefins containing an allylic function that is capable of coordination to osmium.[49] A N_b-benzyloxindole related to chitosenine (**8**) and voachalotine oxindole (**11**), which exhibits the opposite configuration[9] to that of alstonisine (**1**) about the spirojuncture [C(7)], was also prepared by treatment of (−)-N_b-benzyltetracyclic ketone **14a** with osmium tetraoxide reagents that contain bulky amino ligands. Treatment of (−)-N_b-benzyltetracyclic ketone (−)-**14a** with OsO_4/dihydroquinine 4-chlorobenzoate furnished oxindole **24a** with 30:1 diastereoselectivity in 91% isolated yield. The N_b-methyltetracyclic ketone **14b** yielded only one diastereomeric oxindole **24b** in 36−66% isolated yield regardless of the osmium reagent used. From the same optical antipode of tetracyclic ketone (−)-**14a** the synthesis of either the *Alstonia* oxindoles or the *Gardneria* and *Voacanga* oxindole alkaloids [diastereomeric at C(7)] can be pursued. Furthermore, this approach via the inter- versus intramolecular complexation of osmium reagents may be applicable to the diastereoselective conversion of other classes of indole alkaloids into their respective oxindoles. Further work in this area will be reported in the future.

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Table 2. ^{1}H NMR Spectral Data and Assignments for Oxindole 18

chemical shift	appearance	proton
9.84	s, 1H	CHO
7.74	d, J = 7.1 Hz, 1 H	4′
7.37	d, J = 7.2 Hz, 2 H	5′, Bn
7.28	t, J = 7.4 Hz, 2 H	Bn
7.19	m, 2 H	6′, Bn
6.99	t, J = 7.1 Hz, 1 H	Bn
6.71	d, J = 7.7 Hz, 1 H	7′
4.79	d, J = 5.1 Hz, 1 H	13
3.98	m, 2 H	CH_2-Bn
3.85	m, 2 H	14, 15
3.74	m, 3 H	14, 15
3.74	m, 3 H	14, 15, 1
3.14	s, 3 H	N_a-CH_3
2.90	br s, 1 H	5
2.84	bd, J = 10 Hz, 1 H	9
2.58	d, J = 10 Hz, 1 H	9
2.46	ddd, J = 11.7, 5.1, 2.9 Hz, 1 H	2
2.17	dd, J = 13.4 Hz, 7.5 Hz, 1 H	4_{ax}
1.92	m, 1 H	CH_2
1.71	m, 1 H	7
1.51	m, 1 H	CH_2
1.20	m, 1 H	7
1.08	m, 1 H	3
1.00	s, 3 H	CH_3

Experimental Section

Microanalyses were performed on an F and M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with a GE GN500 NMR spectrometer. Ratios of diastereomers were obtained by ^{1}H NMR spectroscopy using a pulse delay of 15 s. The diastereomeric ratios of the mixtures of N_b-benzyloxindoles **21a** to **24a** were determined by ^{1}H NMR spectroscopy (500 MHz, $CDCl_3$) on the purified mixture (flash chromatography) by integration of the N_a-methyl singlets (δ 3.23 for **24a** and δ 3.19 for **21a**) and confirmed by integration of H-7α protons (δ 2.54 for **24a** and δ 2.91 for **21a**). For most reactions the diastereomeric ratios were also determined on the crude product mixtures. In these cases, no significant differences in the **21a**:**24a** ratio were observed between the crude and purified mixtures. Infrared spectra were recorded on a Mattson Polaris IR 10400 spectrometer or a Nicolet MX-1 FT-IR spectrometer. Mass spectral data (EI/CI) were obtained on a Hewlett-Packard 5985B GC–mass spectrometer. High-resolution mass spectra (HRMS) were recorded on a Joel 5 × 102 mass spectrometer under fast atom bombardment conditions (FAB^+) using 3-nitrobenzyl alcohol. Thin layer chromatography was performed with E. Merck Brinkman UV active silica gel (Kieselgel 60 F254 on plastic) or neutral aluminum oxide [aluminum oxide 60 F254 (type E) on plastic], and the plates were visualized with UV light.

All reactions were conducted under an atmosphere of nitrogen. Tetrahydrofuran was distilled from sodium/benzophenone ketyl. The following compounds were obtained from Aldrich Chemical Co. and used without further purification: osmium tetraoxide (**CAUTION: osmium tetraoxide is a volatile, toxic solid!**), quinuclidine, pyridine, hydroquinine 4-chlorobenzoate (DHQ-CLB), hydroquinidine 4-chlorobenzoate (DHQD-CLB), $(DHQD)_2PHAL$, $(DHQ)_2PHAL$. The oxindole, (1*S*,5*S*,6*S*)-1′-methyl-8-benzyl-2-(1′,3′-dioxolan-2′-yl)-3-(1′-ethyloxamethyl)-1,3-spiro[8-azabicyclo[3.2.1]octane-6,3-[3*H*]indole]-2,2′(1′*H*)-dione (**18**), was available from previous work in this laboratory.[27]

Reaction of (±)-N_a,N_b-Dimethyltetracyclic Ketone 14b with Osmium tetraoxide To Provide (±)-(1a,5a,6a)-1′-,8-Dimethylspiro[8-azabicyclo[3.2.1]octane-6,3-[3*H*]indole]-2,2′(1′*H*)-dione (24b). A solution of osmium tetraoxide (48.3 mg, 0.19 mmol) in THF (0.25 mL) was added to a solution of (±)-5-methyl-9-oxo-12-methyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (**14b**)[25] (50 mg, 0.20 mmol) in THF (0.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 2 h and then heated at reflux for 24 h. A solution of $NaHSO_3$ (1.5 g) in H_2O (4 mL) was added to the cooled mixture (0 °C), and the two-phase mixture which resulted was stirred at room temperature for 4 h. This mixture was extracted with EtOAc (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica gel, EtOAc) furnished the starting ketone **14b** (16 mg, R_f = 0.11, EtOAc) and N_b-methyloxindole **24b**: 19.3 mg (36%) (R_f = 0.59, EtOAc); mp 134–136 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (d, J = 7.4 Hz, 1 H, H-4′), 7.27 (t, J = 7.7 Hz, 1 H, H-6′), 7.06 (t, J = 7.4 Hz, 1 H, H-5′), 6.81 (d, J = 7.7 Hz, 1 H, H-7′), 3.53 (m, 1 H, H-1), 3.44 (m, 1 H, $H\text{-}3_{ax}$), 3.24 (s, 3 H, N_a-CH_3), 3.07 (m, 1 H, H-5), 2.60 (s, 3 H, N_b-CH_3), 2.48 (dd, J = 13.6, 8.3 Hz, 1 H, H-7α), 2.37 (d, J = 13.7 Hz, 1 H, H-7β), 2.32–2.18 (m, 3 H, $H\text{-}4_{eq}$, $H\text{-}4_{ax}$, $H\text{-}3_{eq}$); ^{13}C NMR ($CDCl_3$) δ 205.16, 177.62, 142.10, 137.31, 128.00, 123.71, 123.21, 107.50, 106.61, 69.79, 67.18, 55.62, 40.21, 34.46, 34.13, 29.61, 26.51, 23.19; IR (KBr) 2961, 2930, 2852, 1713, 1609, 1081, 817, 803, 750 cm^{-1}; CIMS (CH_4) *m/e* (relative intensity) 271 (100, M + 1); EIMS *m/e* (relative intensity) 270 (M^+, 16), 242 (13), 227 (3), 213 (41), 199 (6), 186 (25), 173 (20), 160 (12), 144 (22), 130 (21), 115 (18), 111 (100), 103 (11); HRMS calcd for $C_{16}H_{18}N_2O_2$ (M + 1) 271.1447, found 271.1457.

Reaction of (±)-N_a,N_b-Dimethyltetracyclic Ketone 14b with Osmium Tetraoxide/Pyridine To Provide (±)-Oxindole 24b. Osmium tetraoxide (47.9 mg, 0.19 mmol) was added to a 0 °C solution of (±)-N_a,N_b-dimethyltetracyclic ketone **14b**[25] (940 mg, 0.16 mmol) in THF–pyridine (2:1, 3 mL) at 0 °C. The mixture which resulted was warmed to room temperature and stirred for 3 days. A solution of $NaHSO_3$ (120 mg) in H_2O (1.2 mL) was then added, and the two-phase mixture which resulted was stirred at room temperature for 4 h. Water (20 mL) was added, and the resultant mixture was extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over K_2CO_3, and concentrated *in vacuo*. Flash chromatography (silica gel, EtOAc) furnished (±)-N_a,N_b-dimethyloxindole **24b** (17 mg, 40%) and the starting ketone **14b** (17 mg).

Reaction of (±)-N_a,N_b-Dimethyltetracyclic Ketone 14b with Osmium Tetraoxide/DHQ–CLB To Provide (±)-Oxindole 24b. A solution of osmium tetraoxide (15 mg, 0.059 mmol) and DHQ–CLB (36.5 mg, 0.079 mmol) in THF (0.2 mL) was added to a solution of (±)-N_a,N_b-dimethyltetracyclic ketone **14b**[25] (10 mg, 0.039 mmol) in THF (0.2 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 days. A solution of $NaHSO_3$ (30 mg) in H_2O (0.3 mL) was then added, and the two-phase mixture that resulted was stirred at room temperature for 4 h. Water (1 mL) was added, and the two-phase mixture was extracted with EtOAc (3 × 25 mL). The organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Chromatography furnished starting ketone **14b** (3.3 mg), DHQ–ClB (25.9 mg, 71% recovery), and (±)-N_a,N_b-dimethyloxindole **24b** (7.0 mg, 66%).

Reaction of (−)-N_a-Methyl-N_b-benzyltetracyclic Ketone 14a with Osmium Tetraoxide/Pyridine To Provide 1-Methyl-8-benzylspiro[8-azabicyclo[3.2.1]octane-6,3-[3*H*]-indole]-2,2′(1′*H*)-diones (21a and 24a). A solution of osmium tetraoxide (942 mg, 3.7 mmol) in THF–pyridine (2:1, 50 mL) was added to a solution of N_b-benzyltetracylic ketone **14a**[25] (1.0 g, 3.0 mmol) in THF–pyridine (2:1, 50 mL) at 0 °C over a 15 min period. The resulting reaction mixture was warmed to rt and stirred for 3 d. A solution of $NaHSO_3$ (12.2 g) in H_2O (40 mL) was added to the reaction mixture (cooled with an ice–H_2O bath). The cooling bath was removed, and the resultant mixture was stirred at rt for 4 h. The aqueous mixture was extracted with EtOAc (5 × 350 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude oil was chromatographed (silica gel, 70:30 hexanes–EtOAc; TLC (50:50 EtOAc–hexanes): R_f = 0.53 for **14a** and R_f = 0.41 for **21a** and **24a**) to give 0.53 g of starting ketone **14a** and 412 mg (36%) of a 1:1 mixture of diastereomeric oxindoles **21a** and **24a**. The diastereomeric oxindoles **21a** and **24a** were then separated by flash chromatography (neutral alumina, CH_2Cl_2).

(1*S*,5*S*,6*R*)-1′-Methyl-8-benzylspiro[8-azabicyclo[3.2.1]octane-6,3-[3*H*]indole]-2,2′(1′*H*)-dione (**21a**): R_f = 0.10, CH_2Cl_2, neutral alumina; mp 91–93 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (m, 2 H, Bn), 7.31 (t, J = 7.5 Hz, 2 H, Bn), 7.26 (t, J = 7.6 Hz, 1 H,

H-6′), 7.22 (t, J = 7.5 Hz, 1 H, Bn), 7.11 (d, J = 7.4 Hz, 1 H, H-4′), 7.02 (t, J = 7.6 Hz, 1 H, H-5′), 6.79 (d, J = 7.7 Hz, 1 H, H-7′), 4.24 (d, J = 12.8 Hz, 1 H, H-9), 4.01 (d, J = 12.8 Hz, 1 H, H-9), 3.72 (d, J = 7.6 Hz, 1 H, H-1), 3.45 (d, J = 6.1 Hz, 1 H, H-5), 3.19 (s, 3 H, N_a-CH_3), 2.91 (dd, J = 13.9, 7.7 Hz, 1 H, H-7α), 2.69 (m, 1 H, H-3_{eq}), 2.60 (m, 1 H, H-3_{ax}), 2.19 (m, 1 H, H-4_{ax}), 2.09 (d, J = 13.9 Hz, 1 H, H-7β), 1.75 (m, 1 H, H-4_{eq}); ^{13}C NMR ($CDCl_3$) δ 212.37 (C, C-2), 180.85 (C, C-2′), 144.05 (C), 138.69 (C), 129.94 (C), 128.57 (CH, C-Bn), 128.50 (CH, C-6′), 128.42 (CH, C-Bn), 128.33 (CH. C-Bn), 127.04 (CH, C-Bn), 123.84 (CH, C-4′), 122.32 (CH, C-5′), 108.04 (CH, C-7′), 70.45 (CH_2, C-1), 64.76 (CH, C-5), 57.23 (C, C-6), 53.63 (CH_2, C-9), 39.53 (CH_2, C-7), 33.88 (CH_2, C-3), 26.51 (CH_3, N_a-Me), 23.08 (CH_2, C-4); IR (KBr) 3058, 3030, 2945, 1709, 1635, 1612, 1494, 1470, 1375, 1350, 1125, 1084, 750, 703 cm^{-1}; CIMS m/e (relative intensity) 347 (100, M + 1); $[\alpha]^{26}_D$ +88.0° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{22}N_2O_2$·1/2EtOAc: C, 73.82; H, 6.71; N, 7.17. Found: C, 73.70; H, 6.39; N, 7.04.

(1*S*,5*S*,6*S*)-1′-Methyl-8-benzylspiro[8-azabicyclo[3.2.1]octane-6,3-[3*H*]indole]-2,2′(1′*H*)-dione (**24a**): R_f = 0.23, CH_2Cl_2, neutral alumina; mp 167−168 °C (HCl salt: mp 101−102 °C); ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 7.4 Hz, 1 H, H-4′), 7.43 (d, J = 7.4 Hz, 2 H, Bn), 7.32 (t, J = 7.4 Hz, 1 H, Bn), 7.28 (t, J = 7.4 Hz, 1 H, H-6′), 7.27 (t, J = 7.4 Hz, 1 H, Bn), 7.12 (t, J = 7.4 Hz, 1 H, H-5′), 6.81 (d, J = 7.4 Hz, 1 H, H-7′), 4.05 (d, J = 13.0 Hz, 1 H, H-9), 3.87 (d, J = 13.0 Hz, 1 H, H-9), 3.70 (br d, J = 7.3 Hz, 1 H, H-1), 3.55 (dt, J = 17.5, 9.8 Hz, 1 H, H-3_{ax}), 3.23 (s, 3 H, N_a-CH_3), 3.16 (br d, J = 4.0 Hz, 1 H, H-5), 2.54 (dd, J = 13.7, 7.3 Hz, 1 H, H-7α), 2.44 (dd, J = 17.5, 8.6 Hz, 1 H, H-3_{eq}), 2.42 (dd, J = 13.7, 0.7 Hz, 1 H, H-7β), 2.29 (m, 1 H, H-4_{ax}), 2.21 (dd, J = 14.5, 9.7, 1 H, H-4_{eq}); ^{13}C NMR ($CDCl_3$) δ 212.44 (C, C-2), 177.18 (C, C-2′), 142.05 (C), 137.52 (C), 137.09 (C), 128.78 (CH, C-11), 128.32 (CH, C-6′), 127.85 (CH, C-12), 127.26 (CH, C-13), 123.48 (CH, C-4′), 122.89 (CH, C-5′), 107.45 (CH, C-7′), 67.53 (CH_2, C-9), 65.09 (CH, C-5), 55.26 (C, C-6), 51.65 (CH, C-1), 39.59 (CH_2, C-7), 34.27 (CH_2, C-3), 26.35 (CH_3, N_a-Me), 23.63 (CH_2, C-4); IR (KBr) 3058, 3030, 2945, 1709, 1637, 1612, 1494, 1469 1375, 1350, 1125, 1084, 750, 700 cm^{-1}; CIMS (CH_4) m/e (relative intensity) 347 (100, M + 1); EIMS m/e (relative intensity) 346 (M^+, 9), 318 (15), 273 (6), 262 (4), 235 (7), 227 (13), 199 (17), 187 (100), 186 (16), 172 (22), 159 (47), 144 (27), 130 (27), 117 (13), 115 (21), 105 (16); $[\alpha]^{26}_D$ +126.0° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{22}N_2O_2$·1/2EtOAc: C, 73.82; H, 6.71; N, 7.17. Found: C, 74.20; H, 6.65; N, 7.11.

Reaction of (−)-N_a-Methyl-N_b-benzyltetracyclic Ketone 14a with 1 Equiv of Osmium Tetraoxide To Provide Oxindole 21a. A solution of osmium tetraoxide (38 mg, 0.15 mmol) in THF (0.5 mL) was added to a solution of N_a-methyl-N_b-benzyltetracyclic ketone **14a**[25] (50 mg, 0.15 mmol) in THF (0.5 mL) at 0 °C. The black mixture which resulted was stirred at 0 °C for 2 h and at reflux for 3 days. The reaction mixture was cooled to rt, and then a solution of $NaHSO_3$ (150 mg) in 1.5 mL of H_2O was added. The resultant mixture was stirred at rt for 4 h. Water (5 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 125 mL). The combined organic extracts were washed with brine (50 mL), dried (K_2CO_3), and concentrated. Flash chromatography (silica gel, 20% EtOAc−hexanes) furnished 24 mg (42%) of a 91:9 mixture of diastereomeric oxindoles **21a**:**24a**.

General Procedure for the Conversion of N_a-Methyl-N_b-benzyltetracyclic Ketone 14a into Oxindoles 21a and 24a Using OsO_4 and Dihydroquinine 4-Chlorobenzoate, Dihydroquinidine 4-Chlorobenzoate, $(DHQD)_2PHAL$, or $(DHQ)_2PHAL$. In a typical experiment, a premixed solution of osmium tetraoxide (57.8 mg, 0.23 mmol) and the amino ligand (0.30 mmol) in THF (1 mL) was added to a solution of N_a-methyl-N_b-benzyl ketone **14a**[25] in THF (1 mL) at rt. The black mixture which resulted was stirred at rt for 3 d. A solution of $NaHSO_3$ (150 mg) in H_2O (1.5 mL) was then added in one portion, and the mixture that resulted was stirred at rt for 4 h. Water (25 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 125 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an off-white residue. The residue was chromatographed (silica gel, 20% EtOAc−hexanes) to give a mixture of oxindoles **21a** and **24a** in 66−91% yields. The amino ligand was recovered by eluting with EtOAc (65−75% recovery).

Reaction of (−)-N_a-Methyl-N_b-benzyltetracyclic Ketone 14a with Osmium Tetraoxide and Dihydroquinine 4-Chlorobenzoate To Provide Oxindole 24a. A premixed solution of osmium tetraoxide (347 mg, 1.4 mmol) and dihydroquinine 4-chlorobenzoate (0.846 g, 1.8 mmol) in THF (3 mL) was added to a solution of (−)-N_a-methyl-N_b-benzyl ketone **14a**[25] in THF (3 mL) at rt. The black mixture which resulted was stirred at rt for 3 d. A solution of $NaHSO_3$ (600 mg) in H_2O (6 mL) was added in one portion, and the mixture which resulted was stirred at rt for 4 h. Water (100 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 400 mL). The combined extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give an off-white residue. The residue was chromatographed (silica gel, 20% EtOAc−hexanes) to give 286 mg (91%) of oxindole **24a** (94% de by ^{1}H NMR spectroscopy). The amino ligand was recovered by eluting with EtOAc (70% recovery).

(±)-5-Methyl-9-oxo-12-benzoyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (12b). Benzoyl chloride (0.11 mL, 0.92 mmol) was added to a solution of (±)-5-methyl-9-oxo-*H*-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole[25] (0.2 g, 0.83 mmol) in anhydrous pyridine (40 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 16 h. Dichloromethane (100 mL) was added and the mixture poured into *aqueous* 2 N HCl (25 mL). The phases were separated, and the organic layer was washed with brine (25 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash chromatography (silica gel, 70% hexanes−EtOAc) furnished N_b-benzoyl ketone **12b**: 165.1 mg (48%); mp 154−156 °C (lit.[50] mp 155−157 °C); ^{13}C NMR (500 MHz, $CDCl_3$) δ 208.02, 170.04, 137.45, 134.51, 132.88, 130.51, 128.81, 126.89, 125.95, 122.26, 122.13, 119.68, 109.17, 106.19, 62.84, 43.59, 34.60, 29.71, 28.44, 26.01; EIMS m/e (relative intensity) 344 (M^+, 12), 287 (4), 223 (6), 201 (11), 195 (11), 183 (21), 182 (10), 168 (14), 129 (7), 105 (100).

Reaction of N_a-Methyl-N_b-benzoyltetracyclic Ketone 12b with Osmium Tetraoxide. A solution of osmium tetraoxide (20.7 mg, 0.081 mmol) in THF (0.8 mL) was added to a solution of (±)-N_a-methyl-N_b-benzoyl ketone **12b** (28 mg, 0.081 mmol) in THF (0.8 mL) at 0 °C. The mixture which resulted was stirred at 0 °C for 2 h, warmed to rt, and stirred for 3 d. A solution of $NaHSO_3$ (80 mg) in H_2O (0.8 mL) was then added to the cooled (0 °C) reaction mixture, and the reaction mixture was stirred at room temperature for 4 h. Water (1 mL) was added, and the resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over K_2CO_3 and concentrated *in vacuo* to give 26.5 mg (95% recovery) of starting N_b-benzoyl ketone **12b** as a white solid.

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