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Enantiocontrolled Synthesis of Spirooxindoles Based on the [5 + 2] Cycloaddition of a Tp(CO)$_2$Mo(pyridinyl) Scaffold (Tp = Hydridotrispyrazolylborate)

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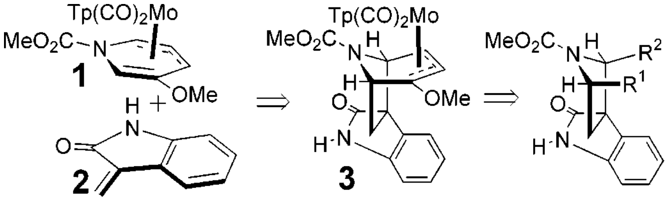
ABSTRACT



A [5 + 2] cycloaddition of the pyridinyl π-complex (–)-1 (98% ee) to methyleneoxindole 2 afforded the spirooxindole complex (–)-3 in high enantiomeric purity. Complex (–)-3 was converted to pyrrolidine (–)-8 (97% ee), which is related to potent cytotoxic analogues of the spirotryprostatins alkaloids.

Stoichiometric transition metal complexes have been used extensively in asymmetric synthesis.[1] Recently, a novel enantiocontrolled route to substituted tropanes was described, which proceeds by way of the [5 + 2] cycloaddition of high enantiomeric purity η^3-pyridinylmolybdenum complexes with electron deficient alkenes.[2] Taking advantage of the significant enantiocontrol inherent in that methodology, we report herein a novel, convergent, and enantiocontrolled synthesis of the core structural unit of the spirooxindole alkaloids using the [5 + 2] cycloaddition of methyleneoxindole **2** to high enantiomeric purity η^3-pyridinylmolybdenum complex (**1**) (Figure 1).

The spirooxindole alkaloids[3] are represented by spirotryprostatin A and alstonisine (Figure 2). Spirotryprostatins and their simpler synthetic analogues, such as that shown in Figure 2, display potent cytotoxic activity.[4] The unique structural features of spirotryprostatins, their medicinal significance, and a limited availability via fermentation have stimulated an intense synthetic activity.[5]

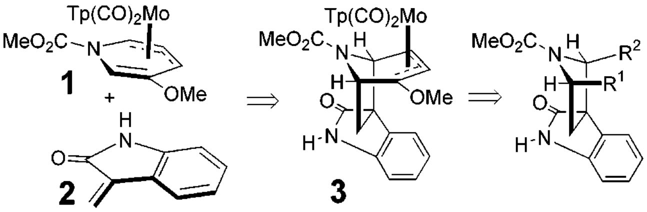


Figure 1. The synthetic strategy.

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[2] Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.*, in press.

[3] For alstonia alkaloids, see: (a) Atta-ur-Rahman, Qureshi, M. M.; Muzaffar, A. *Heterocycles* **1988,** *27*(3), 725−732. For spirotryprostatins, see: (b) Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527−533.

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10.1021/ol000313z CCC: $19.00

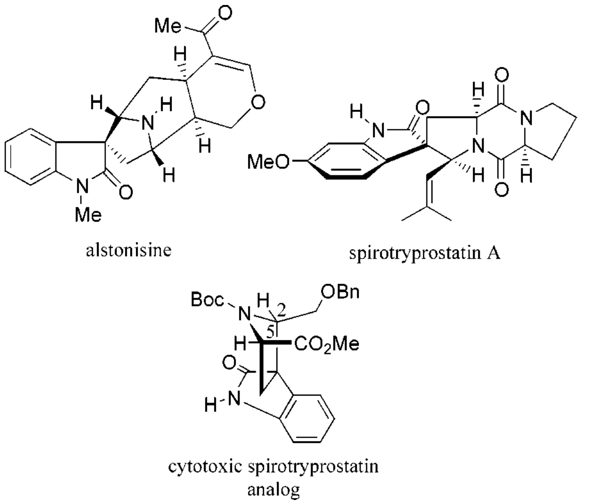
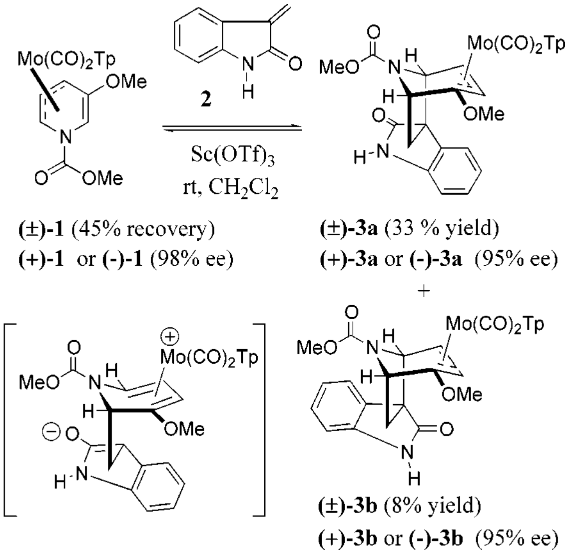


Figure 2. Spirooxindole alkaloids.

Despite the known instability[6] of the unsubstituted[7] methyleneoxindole **2** in concentrated solutions, we anticipated that the mild conditions and fast rate of reaction previously observed in [5 + 2] cycloadditions to the complex **(±)-1**[2] would allow the reaction shown in Figure 1 to proceed. Initial cycloaddition studies were carried out on the racemic complex **(±)-1** (Scheme 1), prepared in six steps from commercially available materials.[2] Treatment of **(±)-1** with oxindole **2**[8] and between 0.5 and 1.4 equiv of EtAlCl$_2$ at room temperature resulted only in recovery of the complex **(±)-1**. A trace (5%) of the cycloadduct **(±)-3a** was isolated when the amount of EtAlCl$_2$ was decreased to 0.2 equiv and the reaction was quenched after 25 min. After some experimentation, we discovered that replacement of EtAlCl$_2$ by the milder Lewis acid Sc(OTf)$_3$[9] provided synthetically useful yields of the desired cycloaddition products. Under optimized conditions (0.2 equiv of Sc(OTf)$_3$, 25−45 min, 2 × 1.3 equiv of **2**, room temperature), a combined 41% yield of the cycloadducts **(±)-3a** and **(±)-3b** with good exo:endo selectivity (4:1, **(±)-3a**:**(±)-3b**) was obtained. Furthermore, 45% of pure complex **(±)-1** was conveniently recovered and recycled, thus bringing the overall yield per converted starting material to 75%.[10] X-ray crystallographic analysis of the major cycloadduct **(±)-3a** allowed an unequivocal assignment of the exo and endo configurations.

The Lewis acid mediated cycloaddition of **1** and **2** appears to be rapid and reversible, possibly proceeding through the intermediate shown in Scheme 1.[2] The cycloadduct yield is dependent on the reaction time and the amount and the nature of the Lewis acid. The stability of the parent methylene-

Scheme 1



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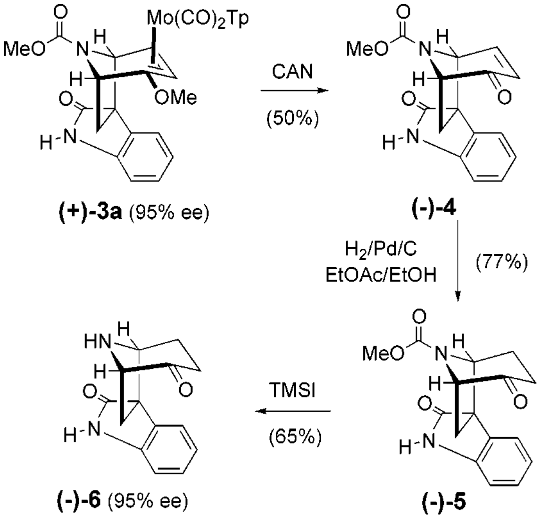
(10) **Experimental procedure for the [5 + 2] cycloaddition:** To the molybdenum complex **(±)-1** (4.52 g, 8.48 mmol), Sc(OTf)$_3$ (0.724 g, 0.1.47 mmol), and methyleneoxindole **2** (1.607 g, 11.087 mmol) was added CH$_2$Cl$_2$ (120 mL). The brown suspension was stirred at room temperature under argon for 10 min. Then a second portion of methyleneoxindole **2** (1.59 g, 10.96 mmol) was added and stirring was continued for 30 min. The reaction mixture was filtered through a short layer of Celite and silica, eluting with EtOAc/hexanes (1:1) to afford the pure unreacted complex **(±)-1** (2.05 g, 45%), and with EtOAc to elute a mixture of two products. The mixture was separated by flash chromatography over silica to afford the molybdenum complex **(±)-3a** (1.909 g, 33%) and a minor product **(±)-3b** (0.407 g, 8%) as bright orange solids. The recovered complex **(±)-1** (2.05 g, 3.84 mmol) was resubjected to the cycloaddition conditions to afford the adduct **(±)-3a** (0.77 g, 30%), adduct **(±)-3b** (0.23 g, 9%), and recovered complex **(±)-1** (0.39 g, 20%). The whole process was repeated once more from the recycled **(±)-1** (0.30 g, 0.56 mmol) to yield the adduct **(±)-3a** (0.132 g, 26%), adduct **(±)-3b** (0.03 g, 7%), and recovered complex **(±)-1** (0.18 g, 45%). Reactions with enantiopure complex **(+)-1** were carried out according to the same procedure in a reaction vessel covered with aluminum foil. Thus, complex **(+)-1** (98% ee, $[\alpha]_D$ = +149°, *c* 0.113 CHCl$_3$) provided the recovered complex **(+)-1** in 98% ee, the molybdenum complex **(+)-3a** in 95% ee ($[\alpha]_D$ = +272°, *c* 0.114 CHCl$_3$), and the complex **(+)-3b** in 95% ee ($[\alpha]_D$ = +337°, *c* 0.090 CHCl$_3$). The complexes **(+)-3a** and **(+)-3b** prepared from the recovered complex **1** (98% ee) retained the enantiomeric excess (95% ee) in both cases. **Analytical data for the molybdenum complex (±)-3a** (a mixture of rotamers arising from the hindered rotation around the C−N bond in the carbamate group): mp = 187−190 °C dec (EtOAc/hexane); R_f = 0.24 (EtOAc/hexane, 1:1). Anal. Calcd for C$_{28}$H$_{27}$BMoN$_8$O$_6$: C, 49.58; H, 4.01; N, 16.52. Found: C, 49.55; H, 3.93; N, 16.26. ^{1}H and ^{13}C NMR data for the isolated, stable single rotamer of **(±)-3a**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.41 (d, J = 1.6 Hz, 1 H), 8.18 (s, 1 H), 8.04 (d, J = 1.6 Hz, 1 H), 7.99 (d, J = 7.2 Hz, 1 H), 7.63 (d, J = 2.4 Hz, 1 H), 7.61 (d, J = 2.0 Hz, 1 H), 7.48 (d, J = 2.4 Hz, 1H), 7.40 (d, J = 2.0 Hz, 1 H), 7.30 (td, J = 7.6 Hz, 1.2 Hz, 1 H), 7.06 (td, J = 7.6 Hz, 1.2 Hz, 1 H), 6.96 (d, J = 8.0 Hz, 1 H), 6.21 (t, J = 2.0 Hz, 1 H), 6.19 (t, J = 2.0 Hz, 1 H), 6.16 (t, J = 2.0 Hz, 1 H), 4.96 (d, J = 6.0 Hz, 1 H), 4.50 (d, J = 3.6 Hz, 1 H), 3.80 (d, J = 7.6 Hz, 1 H), 3.74 (dd, J = 7.6 Hz, 4.0 Hz, 1 H), 3.71 (s, 3 H), 3.42 (s, 3 H), 2.76 (dd, J = 12.8 Hz, 6.4 Hz, 1 H), 2.32 (d, J = 13.2 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 228.6, 227.9, 181.7, 154.7, 146.3, 144.9, 142.0, 140.8, 140.0, 136.5, 136.0, 134.5, 129.2, 128.8, 126.2, 121.8, 110.1, 105.8, 105.7, 105.7, 64.4, 60.0, 59.0, 58.4, 56.8, 54.7, 52.7, 43.4.

oxindole reagent under the reaction conditions does not appear to be a decisive factor in the modest yield, since stable β-substituted methyleneoxindoles give similar yields of cycloadducts.[11] Sc(OTf)$_3$ appears to be generally effective in mediating the formation of highly reversible cycloadducts from very activated olefins.[12] The reversibility of the cycloaddition process was confirmed by treatment of the cycloadduct **(±)-3a** with either EtAlCl$_2$ or Sc(OTf)$_3$ (0.2 equiv) at room temperature in CH$_2$Cl$_2$: mixtures containing the pyridinyl complex **(±)-1** (25−30% mol) and recovered cycloadducts (±)-**3a** (40−50%) and (±)-**3b** (5−8%) were obtained.

The most important feature of the described methodology is the possibility to attach the indole moiety to either enantiotopic face of the pyridinyl ring, since both antipodes of the complex **(±)-1** are equally available.[2] In the present case, the complexes **(+)-1** and **(−)-1** (98% ee, each) afforded the corresponding cycloadducts **(+)-3a**, **(−)-3a** and **(+)-3b**, **(−)-3b** in good enantiomeric excess (95% ee each, Scheme 1). Complexes **(+)-1a** and **(−)-1a** were recovered in 98% ee and, when reused in the [5 + 2] cycloaddition, afforded the products **(+)-3a** and **(+)-3b**, and **(−)-3a** and **(−)-3b**, all in 95% ee.[10] The recovery of high enantiopurity **1** from the cycloaddition reaction attests to the mild reaction conditions used, since acid- and/or light-induced racemization of **1** is known.[2] The reproducible slight loss of enantiomeric purity in the cycloaddition products **3a** and **3b** was puzzling, since the enantiomeric purity of the recovered starting material **1** was not eroded. Therefore, rather than racemization under the reaction conditions, the relatively slow flash chromatography on silica gel required for purification of cycloadducts **3** appeared responsible for the slight decrease in their enantiomeric purity. To test this possibility, a solution of pure **(+)-3a** (95% ee) in ethyl acetate containing an excess of slurried silica gel (flash grade SiO$_2$) was monitored at room temperature over 5 days. Cycloreversion to η^3-pyridinyl complex **1** occurred along with a decrease in the enantiomeric excess of recovered **(+)-3a** to 87%. Neither cycloreversion nor racemization was detected in the absence of silica gel under the same conditions; therefore, the silica gel surface is apparently sufficiently acidic to induce a rapid and reversible cycloaddition with concomitant acid-mediated racemization of **1**.[2] Regardless, the enantiopurity of cycloadducts **3** can be raised; that of **(−)-3a** was increased from 95% to 97% ee by recrystallization from ethyl acetate.

Two synthetic applications of the complex **(±)-3a** were explored. Oxidative demetalation of complex **(±)-3a** was induced by either (NH$_4$)$_2$Ce(NO$_3$)$_6$ (CAN) in 50% yield or by CuCl$_2$ in 60−70% yield[13] and provided the tetracyclic enone **(±)-4** (Scheme 2). Catalytic hydrogenation[14] of **(±)-4** followed by treatment of the ketone **(±)-5** with Me$_3$SiI[15] provided the known amine **(±)-6**,[16] an intermediate in a proposed route to *Alstonia alkaloids*.[3] When the reaction sequence depicted in Scheme 2 was repeated with the complex **(+)-3a** (95% ee), the amine **(−)-6** was obtained in 95% ee. The spectroscopic data for the amine **(−)-6** are consistent with the values reported elsewhere[14b,17] ($[\alpha]_D$ = −49°, c = 0.605 CHCl$_3$; reported $[\alpha]_D$ = −65.9°, c = 1.0, CHCl$_3$, >98% ee). Comparison of the signs of the optical rotation for the amine **(−)-6** confirmed our assignment of the absolute configuration for the complex **(+)-1**[2] as shown by the structure in Scheme 1.

Scheme 2



The tetracyclic enone **(±)-4** appears uniquely suited for the preparation of a variety of spirotryprostatin analogues fitting the structural motif depicted in Figure 2. An oxidative cleavage of the pyridone ring in **(±)-4** would generate a cis 2,5-disubstituted pyrrolidine, exclusively. In the event, Luche

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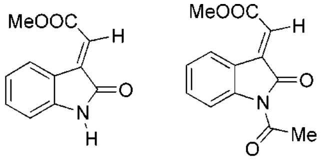
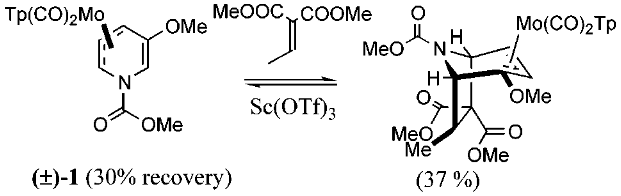
(11) Under EtAlCl$_2$ and Sc(OTf)$_3$ catalysis, the [5 + 2] cycloaddition of the complex **(±)-1** with the stable β-substituted oxindoles shown below did not afford improved yields of the cycloadducts.



(12) For example, the EtAlCl$_2$-mediated reaction of the complex **(±)-1** with dimethyl ethylidenemalonate failed, while 37% yield of the cycloadduct was isolated when Sc(OTf)$_3$ (0.27 equiv) was used as the catalyst.



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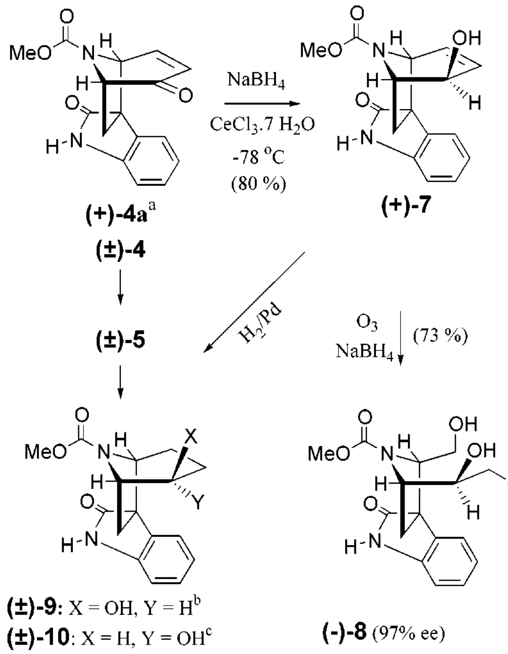
(17) Personal communication from Professor James Cook, University of Wisconsin at Milwaukee.

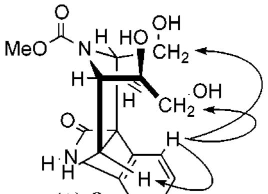
Scheme 3



[a] From **(−)-3a** (97% ee) treated with CuCl$_2$, THF, room temperature (71% yield). [b] From **(±)-7** treated with H$_2$ (1 atm), Pd/C, EtOH, rt, 10h (76% yield). [c] From **(±)-5** treated with L-Selectride (1.1 equiv), THF, −78 °C, 50 min (56%).

reduction[18] of enone **(±)-4** yielded the allylic alcohol **(±)-7**, presumably via delivery of hydride from the more sterically hindered face[19] (Scheme 3). To ascertain the diastereomeric purity of allylic alcohol **(±)-7**,[20] it was catalytically hydrogenated to **(±)-9**, whose diastereomeric purity was confirmed by an independent preparation of isomer **(±)-10**, which is epimeric at C-3. The saturated alcohol **(±)-10** was prepared by reduction of the ketone **(±)-5** with L-Selectride,[21] resulting in hydride delivery from the less hindered face. The saturated alcohol **(±)-9**, obtained by catalytic hydrogenation of **(±)-7**, was produced as a single diastereomer without a detectable trace of the C-3 epimer **(±)-10** in the crude reaction mixture (TLC and NMR analyses).

Ozonolysis[22] of allylic alcohol **(±)-7** and reductive work up (NaBH$_4$) afforded the pyrrolidine **(±)-8** as a single isomer in good yield (Scheme 3). The desired cis stereochemical relationship of the oxindole aryl ring and the substituents at carbons C-2 and C-5 in **(±)-8** was confirmed by a 2D ^{1}H NMR NOESY experiment (Figure 3).



(±)-8

Figure 3. Correlations Detected by NOESY of (±)-**8**

According to the same protocol, enone **(+)-4**, obtained in 71% yield by CuCl$_2$-mediated demetalation of the complex **(−)-3a** (97% ee), afforded pyrrolidine **(−)-8** in 97% ee (Scheme 3).[23] Evaluation of the biological activity of pyrrolidine **8** will be independently pursued.

In conclusion, using η^3-pyridinylmolybdenum complex (**1**) as a chiral scaffold, [5 + 2] attachment of methylene-oxidinole **2** generated in a single step cycloadduct **3** bearing the three chiral centers of the spirooxindole skeleton and, furthermore, established unequivocally the cis configuration of the two substituents at carbons C-2 and C-5 in the pyrrolidine ring. The versatility of the synthon **3** has been demonstrated by its conversion to the amine **(−)-6** (95% ee) (Scheme 2), previously prepared by Cook et al. from D-(+)-tryptophan[16] as a building block for *Alstonia* alkaloids,[3] and to the pyrrolidine **(−)-8** (97% ee) (Scheme 3) structurally related to the cytotoxic simple spirotryprostatin analogue shown in Figure 2, above.[4]

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Supporting Information Available: Complete experimental description, compound characterization, and X-ray crystallographic studies of compound **3a**. Includes photocopies of ^{1}H and ^{13}C NMR spectra for compounds **4-10** and the [5 + 2] cycloadduct of **(±)-1** with dimethyl ethylidene-malonate. COSY and NOESY spectra for **8**. Chiral phase HPLC chromatograms of **(±)-4**, **(+)-4**, **(±)-6**, **(−)-6**, **(±)-8**, **(−)-8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) ^{1}H and ^{13}C NMR data of **(±)-7** are highly complex, showing two sets of signals for each carbon and proton at room temperature. Increasing the temperature for the NMR experiments to 60 °C resulted in significant peak broadening.

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(23) The structures of compounds (+)-**4**, (+)-**7**, (−)-**8**, shown in Scheme 3, correspond to the mirror images of the actual enantiomers.