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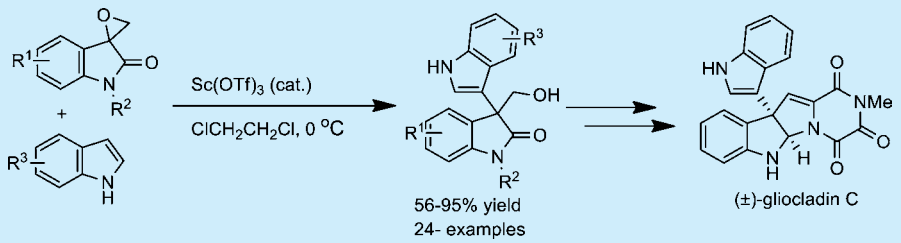
Efficient Synthesis of 3,3′-Mixed Bisindoles via Lewis Acid Catalyzed Reaction of Spiro-epoxyoxindoles and Indoles

Saumen Hajra,*[,†,‡] Subrata Maity,[†,‡] and Ramkrishna Maity[†]

[†]Centre of Biomedical Research, Sanjay Gandhi Post-Graduate Institute of Medical Sciences Campus, Raebareli Road, Lucknow 226014, India

[‡]Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, India

Supporting Information



ABSTRACT: An efficient strategy for the synthesis of 3-(3-indolyl)-oxindole-3-methanol has been developed to achieve a Lewis acid catalyzed, highly regioselective ring opening of spiro-epoxyoxindoles with indoles. The method is used for the gram-scale formal total synthesis of (±)-gliocladin C.

3,3′-Bisindole, in particular, 3a-(3-indoyl)-hexahydropyrrolo-[2,3-*b*]indole, is a unique structural skeleton present in and precursor to many indole alkaloids (Figure 1).[1,2] The rigid

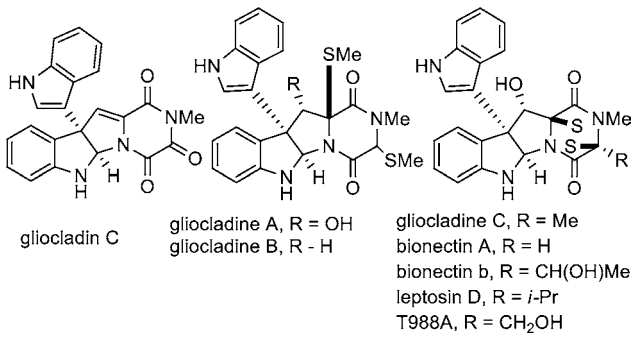


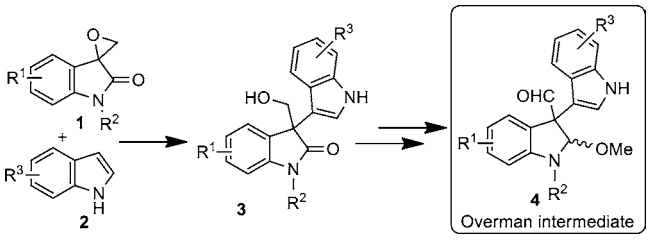
Figure 1. Representative natural 3a-(3-indoyl)-hexahydropyrrolo[2,3-*b*]indole alkaloids.

tetracyclic subunit and a quaternary stereogenic center at the bridge-head are the key structural signatures of the alkaloids, which are endowed with remarkable biological and pharmacological activities. The interesting molecular architecture and biological properties of the compounds have drawn much attention from synthetic chemists worldwide.[3−6]

Therefore, much effort has been devoted toward the development of efficient methods for the synthesis of 3,3′-bisindole containing a C3-all carbon quaternary center such as the (i) Mukaiyama-aldol reaction of 3-(3-indolyl)-2-siloxyindole with aldehyde;[4a] (ii) acyl migration of indolyl carbonates;[7] (iii) Pd-catalyzed allylic alkylation of 3-aryl-3′-oxindoles with allenes;[8] (iv) organo-catalytic conjugate addition of indoles to isatin derived nitroalkenes and α,β-unsaturated aldehydes;[9] (v) α-alkylation of carbonyl compounds with 3-hydroxy-3-indol-3′-yloxindoles;[10] and (vi) Rh-catalyzed multicomponent reaction of 3-diazooxindoles, indoles, and aldehydes.[11]

Another efficient strategy could be the regioselective ring opening of easily accessible spiro-epoxy oxindoles[12] **1** with indoles **2** (Scheme 1). There are several reports on Friedel−

Scheme 1. Proposed Designed Reaction of Spiro-epoxyoxindoles and Indoles



Crafts type reactions of epoxides, in particular, with indoles.[13] However, ring-opening reactions of spiro-epoxyoxindoles[14] have not been explored, in particular, with carbonnucleophiles to construct the oxindoles with a C3-quaternary stereocenter. More importantly, the strategy would provide an easy access to the Overman intermediate, 3-(3-indolyl)-oxindole-3-carbaldehyde **4**.[4b,c] Our continuing interest[15] in exploring the reactivity of three-membered reactive intermediates led us to investigate the Friedel−Crafts type reaction of spiro-epoyoxindoles with

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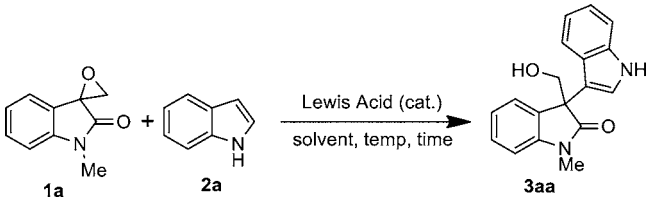
indoles. Herein we report an efficient and straightforward synthesis of 3-(3-indolyl)-oxindole-3-methanol **3** via metal triflate catalyzed regioselective ring opening of spiro-epoxy oxindoles **1** with indoles **2** and a concise gram-scale formal total synthesis of (±)-gliocladin C.

To probe the validity of our envisioned design for the regioselective ring opening of spiro-epoxyoxindoles with indoles, we studied a model reaction between *N*-methyl-spiro-epoxyoxindole **1a** with indole **2a**. To optimize the reaction conditions, the Friedel-Craft type reactions of **1a** and **2a** were carried out by varying the metal triflates, temperature, and solvents (Table 1). In the event, $Sc(OTf)_3$ catalyzed

Table 1. Optimization of Reaction Conditions[a]



entry	Lewis acid	solvent	temp (°C)	time (h)	yield[b] (%)
1	$Cu(OTf)_2$	CH_2Cl_2	25	36	28
2	$In(OTf)_3$	CH_2Cl_2	25	30	30
3	$Sc(OTf)_3$	CH_2Cl_2	25	6.5	41
4	$Cu(OTf)_2$	CH_2Cl_2	0	62	41
5	$In(OTf)_3$	CH_2Cl_2	0	20	45
6	$Mg(OTf)_2$	CH_2Cl_2	0	72	NR
7	$Y(OTf)_3$	CH_2Cl_2	0	85	37
8	$Sm(OTf)_3$	CH_2Cl_2	0	70	45
9	$Sc(OTf)_3$	CH_2Cl_2	0	8	48
10	$Sc(OTf)_3$	DCE	25	3	70
11	**$Sc(OTf)_3$**	DCE	**0**	**4**	**95**
12	$In(OTf)_3$	DCE	0	8	85
13	$Sc(OTf)_3$	THF	0	22	52
14	$Sc(OTf)_3$	$CHCl_3$	0	21	72
15	$Sc(OTf)_3$[c]	DCE	0	12	85

[a]*N*-Methyl spiro-epoxyoxindole **1a** (0.28 mmol), indole **2a** (0.85 mmol), and Lewis acid (10 mol %) in solvent (2 mL) were stirred at specified temperature. [b]Isolated yield. [c]5 mol % of $Sc(OTf)_3$; NR: No reaction. **3aa**: the first letter "a" originates from structure **1a**, and the second letter "a" originates from structure **2a**.

reaction in dichloroethane (DCE) at 0 °C gave exclusively the desired product **3aa** with an excellent isolated yield (95%; entry 11). Reactions conducted under other conditions showed either no reaction or slow reaction with low to moderate yields along with a mixture of uncharacterized compounds. $In(OTf)_3$ also showed a comparable yield in DCE at 0 °C (entry 12).

This method could produce a large number of 3-hydoxymethyl-3-(3-indolyl)-oxindoles **3**, if different combinations of spiro-epoxyoxindoles and indoles are reacted. Thus, to test the generality of this method, a series of spiro-epoxyoxindoles and indoles were investigated under the optimized reaction conditions (Figure 2). Electron-donating and -withdrawing substituents at C5 and C7 of the epoxyoxindoles were evaluated. Unsubstituted *N*-methyl epoxyoxindoles **1a** underwent smooth reactions with three different indoles **2a**−**c** and gave very good to excellent yields of bisindoles **3aa**−**3ac**. An indole with electron-donating substituent **2b** underwent faster reaction. In comparison, substituted *N*-methyl epoxyoxindoles **1b**−**1f** took more time

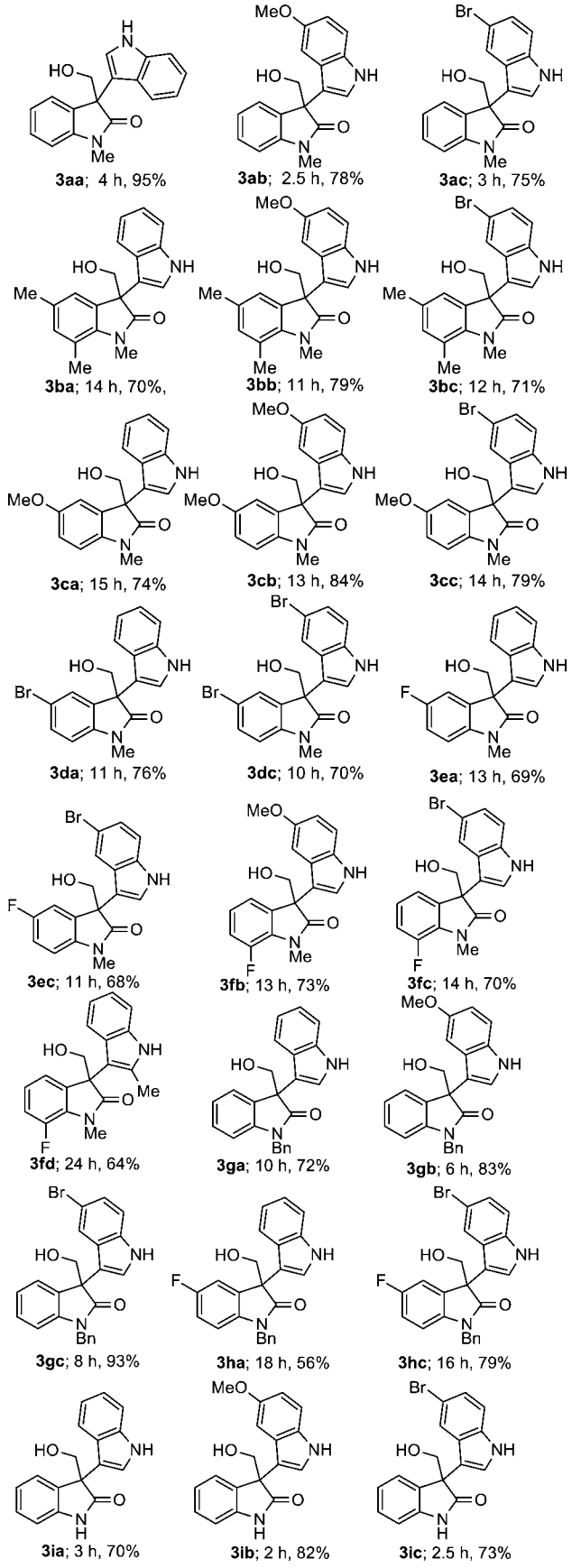


Figure 2. Substrate scope; the first set of letters of **3aa**−**3ic** originates from structures **1a**−**i**, and the second set from structures **2a**−**c**.

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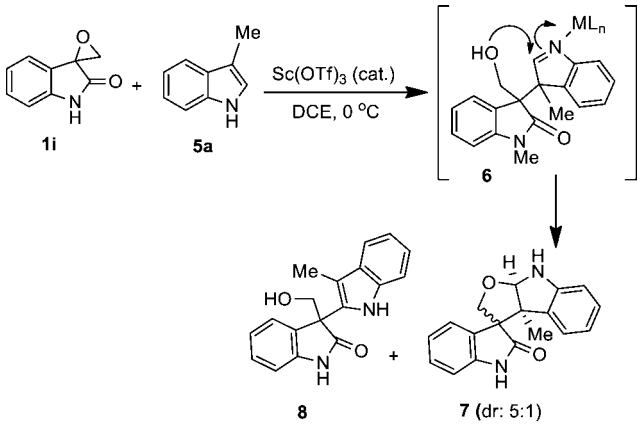
for complete conversion irrespective of the nature of substituents and their position giving good yields of compounds **3ba**–**3fc**. An epoxyoxindole such as **1f** also reacted well with 2-methylindole and gave a good yield of bis-indole **3fd**, but the reaction was slow. Changing the N-protecting group was also studied. *N*-Benzyl epoxy oxindoles **1g** and **1h** were found to take more time in comparison with the corresponding *N*-methyl epoxyoxindoles **1a** and **1e**. The reaction was also evaluated with the spiro-epoxy oxindoles without *N*-protection. Protection-free epoxyoxindoles **1i** underwent smooth reaction and afforded a very good yield of bisindoles **3ia**–**ic**. Overall the unprotected substrates showed faster reactivity than the N-protected substrates.

Reaction of epoxyoxindole **1** with 3-substituted indole might provide the bisindole with vicinal all-carbon quaternary centers. Accordingly, compound **1i** was reacted with 3-methylindole **5a** under the same reaction conditions (Scheme 2). Interestingly,

Scheme 2. Reaction of Spiro-epoxyoxindole 1i and 3-Methylindole 5a

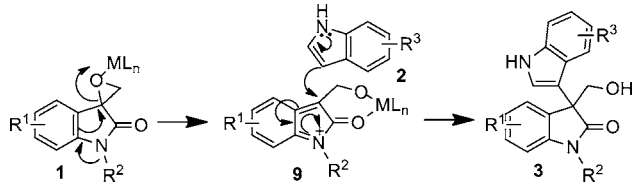


it gave tetrahydrospirofuro-bisindole **7** having vicinal all-carbon quaternary centers as a diastereomeric mixture along with 2,3-bisindole **8**. It seems epoxide opening with 3-methylindole followed by intramolecular cyclization of the intermediate imine **6** afforded the tricyclic tetrahydrofuroindole core.

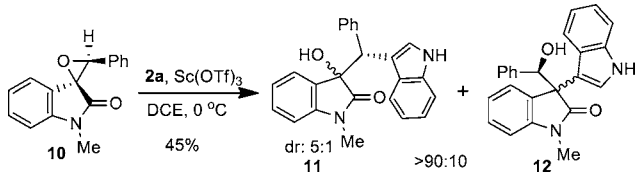
Mechanistically, the reaction of spiro-epoxyoxindole **1** and indole **2** can proceed through 2*H*-indol-2-one **9** formed upon treatment of epoxyoxindole with a Lewis acid (Scheme 3).[16] The indole **2** can easily add to the intermediate **9** to afford the bisindoles **3** with excellent regioselectivity.

The reaction of trisubstituted spiro-epoxyoxindole[12j] **10** having two possible reactive sites was also investigated (Scheme 4). Interestingly it gave compound **11**, raised from the less substituted benzylic center attack as a major product compare to product **12** through an indole-2-one intermediate. The reaction was found to be very slow with incomplete conversion.

Scheme 3. Proposed Mechanism for the Lewis Acid Mediated Reaction of Spiro-epoxyoxindoles and Indoles

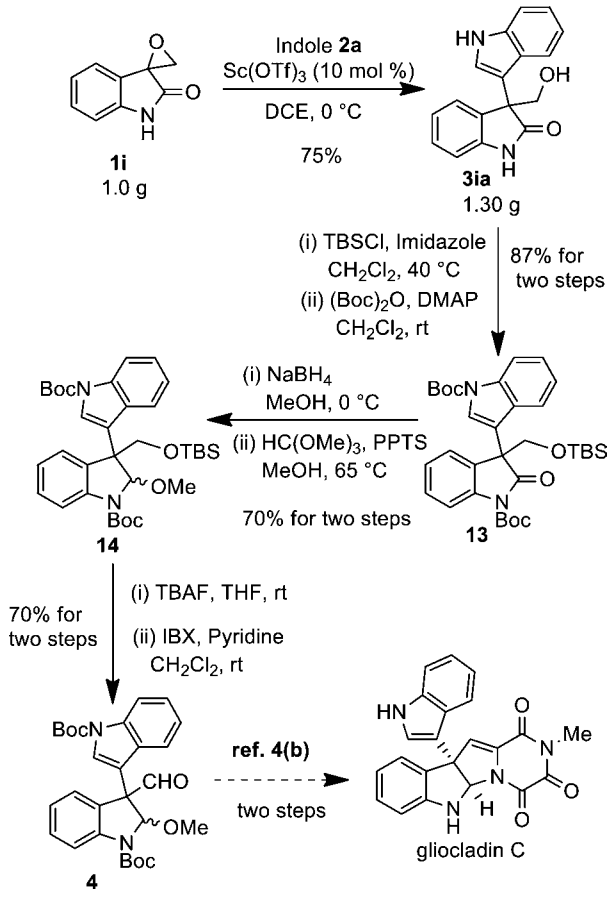


Scheme 4. Reaction of Trisubstituted Spiro-epoxyoxindole 10 and Indole 2a



The synthetic potential and utility of this method was further demonstrated by a gram-scale formal total synthesis of (±)-gliocladin C (Scheme 5). For this purpose a gram-scale

Scheme 5. Formal Total Synthesis of (±)-Gliocladin C



ring opening reaction of spiro-epoxy oxindole **1i** with indole **2a** under optimized conditions was performed and gave bis-indole methanol **3ia** in 75% yield, higher than the small scale reaction. *N*- and *O*-Protection of the bisindole **3ia** afforded the compound **13**. The oxindole carbonyl of **13** was reduced with $NaBH_4$ at 0 °C followed by treatment with a methanolic solution of trimethyl orthoformate, and a catalytic amount of PPTS provided indoline *N,O*-acetal **14**. Desilyation and IBX oxidation of the (3-(1*H*-indol-3-yl)-2-methoxyindolin-3-yl)-methanol **14** gave a very good yield of the Overman intermediate **4**, a versatile precursor for the synthesis of bisindole alkaloids.[4] In an additional two steps, the Overman intermediate **4** could be transformed to (±)-gliocladin C.[4a]

In summary, we have developed a highly efficient, versatile protocol for the synthesis of 3-(3-indolyl)-oxindole-3-methanols via the $Sc(OTf)_3$ catalyzed, highly regioselective ring

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opening of a variety of spiro-epoxy oxindoles with indoles. The method is also suitable for the protection-free spiro-epoxyoxindoles, and it undergoes faster reaction in high yield. The ring opening reaction is easily scaled up to gram scale. One of the 3-(3-indolyl)-oxindole-3-methanols is efficiently transformed to the Overman intermediate, allowing the gram-scale formal total synthesis of (±)-gliocladin C. Further studies on the utility of the spiro-epoxyoxindoles and their applications are currently being investigated in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic and analytical data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01432.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: saumen.hajra@cbmr.res.in.

Notes

The authors declare no competing financial interest.

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