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# A NEW METHOD FOR EFFICIENT COUPLING OF INDOLE AND EPOXIDE CATALYZED WITH YB(OTF)$_3$, AND APPLICATION TO THE TOTAL SYNTHESIS OF KURASOIN B

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**Abstract** – The Yb(OTf)$_3$ catalyzed reaction between indole and epoxide in simple and mild condition was developed. This method is suitable for gram-scale synthesis of 3-indolelactic acid derivatives. The asymmetric synthesis of kurasoin B was achieved using chiral 3-indolelactic acid methyl ester as the starting material.

The coupling reaction between indole and epoxide, in the presence of Lewis acid, to obtain 2-(3-indol)ethanol derivatives is well-known as an efficient process in synthetic chemistry.[1] Although it is easy to form carbon-carbon bonds, this type of reaction relies upon the reactivity of the epoxide, with Lewis acid as the activator. The first reported coupling reaction between indole and 2,3-epoxybutyrate for the total synthesis of indolemycin was successful in the presence of $SnCl_4$, but the yield was not particularly good.[1]

During our study of neoxaline, the indole alkaloid isolated from *Aspergillus japonicus* Fg-551, the asymmetric synthesis of 3-indolelactic acid methyl ester [**(+)-3**] was necessary to produce a suitable starting material.[2] The most efficient way to prepare this would be by using the coupling reaction between indole and chiral methyl glycidate[3] (**2**) in the presence of Lewis acid. However, to our knowledge, there is no reported means to synthesize **3** by the same type of coupling reaction.

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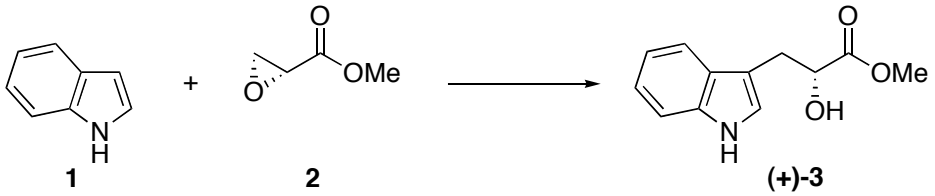
This paper is dedicated to Professor Yoshito Kishi on the occasion of his 70$^{th}$ birthday.

Using a common method (stoichiometric $SnCl_4$, –5 °C) in the first instance gave the desired compound [**(+)-3**] in moderate yield, but complicated purification was subsequently required due to including unknown byproducts derived from destroyed **1** and **2**. This method is therefore not suitable for large-scale synthesis. Kotsuki[4] employed $Yb(OTf)_3$ under high pressure, which although effective, proved difficult and unable to make the amount of material needed. Consequently, we sought a method that would provide higher yields (Table 1).

Table 1. The coupling reaction between indole and methyl glycidate.




**1** **2** **(+)-3**

| Entry | Indole (**1**) | Epoxide (**2**) | Lewis acid | Solvent (conc.) | Temp. | Time | Yield |
|---|---|---|---|---|---|---|---|
| 1 | 1.0 eq | 1.2 eq | $SnCl_4$ (2.0 eq) | $CCl_4$ (0.1 M) | –5 °C | 1 h | 52% |
| 2 | 1.0 eq | 1.2 eq | $Sc(OTf)_3$ (0.1 eq) | 1, 2-dichloroethane (0.1 M) | 80 °C | 24 h | Complex Mixture |
| 3 | 2.0 eq | 1.0 eq | $Cu(OTf)_3$ (0.1 eq) | 1, 2-dichloroethane (0.1 M) | 80 °C | 50 min | 21% |
| 4 | 1.0 eq | 1.2 eq | $Yb(OTf)_3$ (0.1 eq) | $CH_2Cl_2$ (0.1 M) | 40 °C | 66 h | 17% |
| 5 | 1.0 eq | 1.2 eq | $Yb(OTf)_3$ (0.1 eq) | 1, 2-dichloroethane (0.1 M) | 80 °C | 24 h | 39% (indole;59% ) |
| 6 | 1.0 eq | 1.2 eq | $Yb(OTf)_3$ (0.1 eq) | 1, 2-dichloroethane (0.5 M) | 80 °C | 24 h | 52% |
| 7 | 2.0 eq | 1.0 eq | $Yb(OTf)_3$ (0.1 eq) | 1, 2-dichloroethane (0.5 M) | 80 °C | 1 h | 77% |

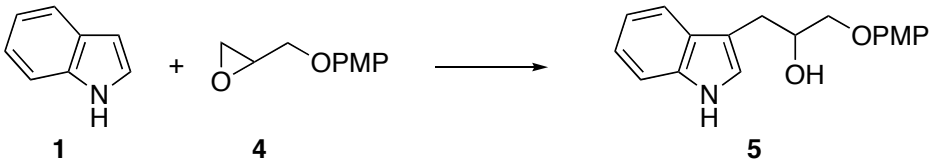
Since lanthanoid is useful for this type of reaction, we started to use $Sc(OTf)_3$,[5] and $Cu(OTf)_2$.[6] These conditions afford a complex mixture in heat condition while result very low conversion at room temperature. (Entries 2,3). Use of $Yb(OTf)_3$ in $CH_2Cl_2$ at room temperature gave a poor result (Entry 4). Changing the solvent to 1,2-dichloroethane to treat it at higher temperature affords **(+)-3** in 39% (recovered indole; 59%). In this case, although the reaction condition is stronger, indole is not destroyed. Decreased yields are thought to be due to weak epoxide to Lewis acid (Entry 5). Increased concentrations cause high indole reactivity, resulting in improved yield (Entry 6). Moreover using excess indole produced a better yield (Entry 7).[8]

The optimized conditions allowed gram-scale synthesis, and we subsequently achieved the construction of spiroaminal in neoxaline.[2]

We then investigated the scope and limitation of this method. Several epoxides were examined. Although PMP glycidyl ether (**4**)[7] was applied under the same condition as making **(+)-3**, similar results could not

be achieved because of the non-positional selectivity of the indole's attack. This result suggests that the lone pair on the oxygen of carbonyl group would coordinate ytterbium (Scheme 1).

Scheme 1. The coupling reaction with glycidyl ether.




**1** **4** **5**

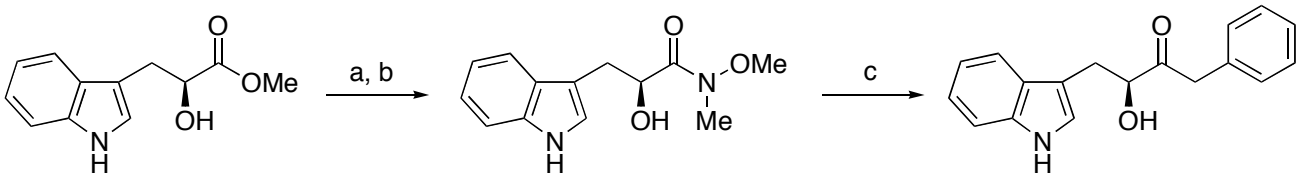
Reagent and conditions: $Yb(OTf)_3$ (0.1 eq), indole (2.0 eq), glycidyl PMP ether (1.0 eq), 1,2-dichloroethane, 60 °C, 2.5 h (22%).

Having developed an efficient way to make **3** in acceptable quantities, we considered that this method might be utilized as a chiral building block for the synthesis of another indole natural product.

In the 1990's, kurasoin B (**7**) was isolated as a farnesyltransferase inhibitor in the Kitasato Institute.[9] The structure of this compound was determined by the racemic synthesis of **7,** as there was no efficient method to make chiral indolelactic acid derivatives at that time. Asymmetric total synthesis of **7** was achieved *via* Sharpless kinetic resolution as a chiral induction, in addition to the coupling reaction between indole and corresponding epoxides, which has some unfortunate drawbacks.[10] With a better way to make **3**, we tried to improve the total yield in the synthesis of **7** (Scheme 2).

3-Indolelactic acid methyl ester [**(–)-3**] was hydrolyzed and amidated to obtain the Weinreb amide (**6**). The alkylation of **6** with benzyl magnesium bromide in diethyl ether solution achieved the asymmetric total synthesis of kurasoin B (in 60% total yield) from **(–)-3**.

Scheme 2. Total synthesis of kurasoin B from **(–)-3**.




**(–)-3** **6** kurasoin B (**7**)

Reagent and conditions: (a) 0.2 N KOH in EtOH:$H_2O$ (4:1), rt, 12hr, (b) EDCI, HOBt, *i*$Pr_2Et$, *N*,*O*-dimethylhydroxylamine•HCl, rt, 21 h, 2 steps 86%, (c) BnMgBr in $Et_2O$, 6 h, rt, 90%.

In summary, we developed a simple method to synthesise the chiral 3-indolelactic acid methyl ester (**3**) *via* the coupling reaction with indole and the chiral methyl glycidate (**2**). The chiral **3** quantities available as starting material for natural product synthesis allowed us to achieve the revised total synthesis of kurasoin B (**8**).

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7. **(+)-3**; R*f* = 0.26 (Hexane/ EtOAc=1:1); mp = 65-67 °C; $[\alpha]_D^{22}$ = +23.4° (*c* = 1.22 in $CHCl_3$); IR (KBr) n $cm^{-1}$ = 3344, 3054, 2949, 1732, 1620, 1437, 1352, 1180, 1093, 1009, 974, 741, 652; $^1$H-NMR (270 MHz, $CDCl_3$) d = 8.07 (br-s , 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.32-7.10 (m, 2H), 7.10 (s, 1H), 4.53 (dd, *J* = 5.6Hz, 4.6 Hz, 1H), 3.72 (s, 3H), 3.31 (dd, *J* = 14.5, 4.6 Hz, 1H), 3.19 (dd, *J* = 14.5, 5.6 Hz, 1H), 2.76 (br-s, 1H); $^{13}$CNMR (67.5 MHz, $CDCl_3$) d = 174.7, 136.0, 127.4, 123.3, 121.9, 119.3, 118.6, 111.2, 109.7, 70.7 , 52.3, 30.2 ; HR-MS (FAB, NBA matrix) *m/z*: 219.0900 $[M]^+$, calc for $C_{12}H_{13}NO_3$: 219.0895[M]. **(–)-3**; $[\alpha]_D^{22}$ = –26.1° (*c* = 0.96 in $CHCl_3$).
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