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Ytterbium(III) Trifluoromethanesulfonate Catalyzed High Pressure Reaction of Epoxides with Indole. An Enantioselective Synthesis of (+)-Diolmycin A2[1]

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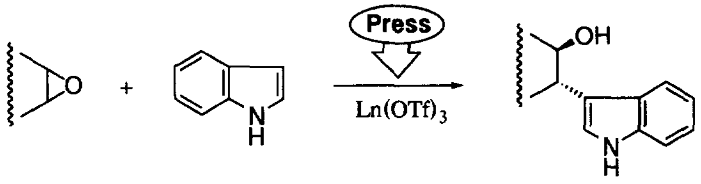
Abstract: Epoxide opening reactions with indole are efficiently accelerated under high pressure conditions in the presence of a catalytic amount of ytterbium(III) trifluoromethanesulfonate to afford tryptophol derivatives. The procedure is successfully applied for an enantioselective synthesis of (+)-diolmycin A2. Copyright © 1996 Elsevier Science Ltd

Recently we reported that epoxide ring opening reactions with a variety of nitrogen heterocycles were efficiently promoted at high pressure.[1,2] Although the synthetic utility of this procedure is apparent from its fairly mild conditions without the use of any catalysts, the main drawback is the low reactivity of indoles toward less reactive epoxides such as aliphatic ones. In our extensive efforts to overcome this difficulty, we found that silica gel could serve as an unprecedented solid acid catalyst,[1] but a more efficient method to expand its synthetic value still remains to be designed.

In view of the increasing importance of lanthanide(III) trifluoromethanesulfonates [lanthanide triflates, $Ln(OTf)_3$] as unusually strong Lewis acids in organic synthesis,[3] we expected that high pressure reaction of epoxides with indole might be also facilitated by the assistance of these catalysts (eq. 1).[4,5] In this paper we would like to describe the realization of this expectation and its successful application to an enantioselective synthesis of (+)-diolmycin A2.[6]



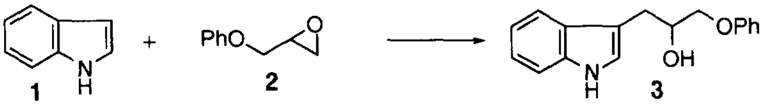
(1)

We examined a number of different types of catalysts for the reaction of indole (**1**) and glycidyl phenyl ether (**2**). The results are summarized in Table 1.[7] Thus, compared with the previous examples (runs 1 and 2),[1] the use of $Yb(OTf)_3$ or $PhB(OH)_2$ was highly effective for the present transformation (runs 3-15). As expected, p-TsOH•H_2O acted as a rather drastic Brønsted acid accompanied with significant decomposition of the starting epoxide **2** (run 19). LiOTf and $Eu(fod)_3$ showed only modest reactivity (runs 16-18).

The Yb(III)-catalyzed reaction was also effective even in refluxing CH_2Cl_2 at atmospheric pressure, but under these conditions the reaction was mostly slow and contaminated by complex byproducts (runs 3 and 4).

Again we could recognize that the high pressure technique is indeed convenient in promoting this type of nucleophilic ring opening process.[8] In accordance with the results observed by Crotti, et al.,[4b,c] the reaction in CH_3CN was rather slower than in the case of CH_2Cl_2 or toluene (e.g., compare runs 5, 6 and 7). Interestingly, addition of a small amount of water in these systems could improve the product yield (runs 10-12). These results imply increased oxophilicity of the Yb(III) catalyst to an epoxide ring oxygen by releasing the active Yb^+ species.[3,4b,c] As a consequence, the reaction system composed of $Yb(OTf)_3$ as catalyst and wet CH_2Cl_2 as solvent represents the most satisfactory procedure for our purpose (runs 11 and 12).

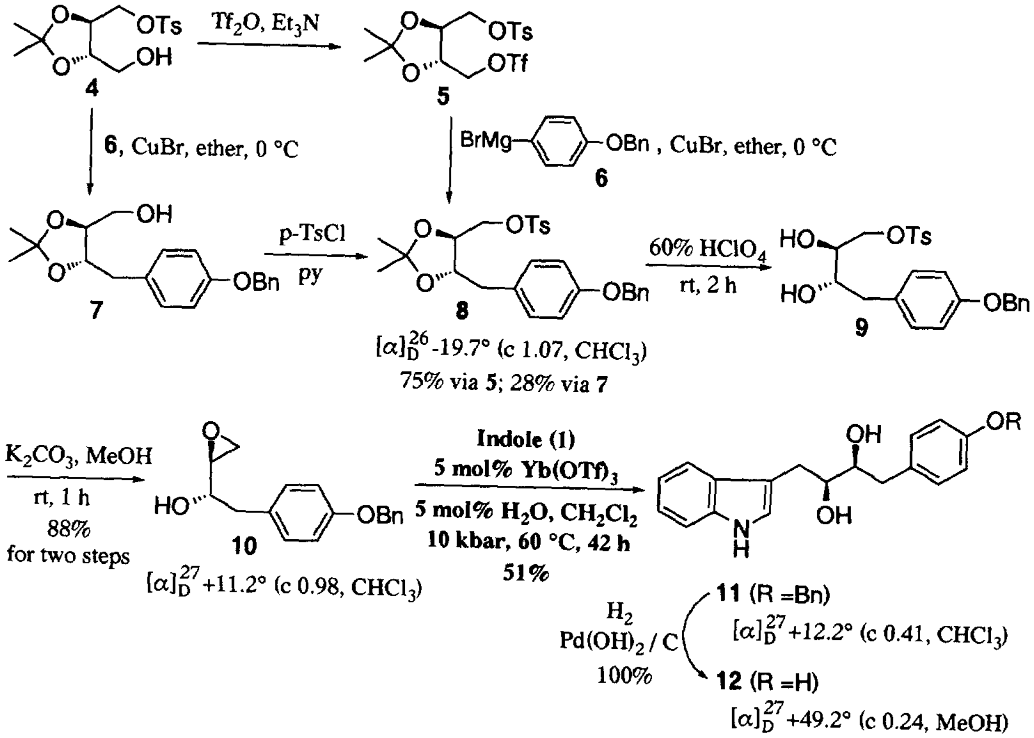
Table 1. High Pressure-Promoted Reaction of Indole (**1**) with Glycidyl Phenyl Ether (**2**)[a]



Run	Solvent	Additive	Reaction Conditions	Yield, %[b]
1	CH_3CN	none	10 kbar, 60 °C, 3 days	16[c]
2	CH_3CN	SiO_2 (LC-5H, 1000 mg / mmol)	10 kbar, 60 °C, 3 days	29[c]
3	CH_3CN	5 mol% $Yb(OTf)_3$	1 atm, reflux, 9 days	19
4	CH_2Cl_2	5 mol% $Yb(OTf)_3$	1 atm, reflux, 9 days	59
5	CH_3CN	5 mol% $Yb(OTf)_3$	10 kbar, 60 °C, 42 h	30
6	CH_2Cl_2	5 mol% $Yb(OTf)_3$	10 kbar, 60 °C, 42 h	52
7	Toluene	5 mol% $Yb(OTf)_3$	10 kbar, 60 °C, 42 h	56
8	CH_3NO_2	5 mol% $Yb(OTf)_3$	10 kbar, 60 °C, 42 h	33
9	THF	5 mol% $Yb(OTf)_3$	10 kbar, 60 °C, 42 h	NP[d]
10	CH_3CN	5 mol% $Yb(OTf)_3 + H_2O$	10 kbar, 60 °C, 42 h	46
11	**CH_2Cl_2**	**5 mol% $Yb(OTf)_3 + H_2O$**	**10 kbar, 60 °C, 42 h**	**58**
12	**CH_2Cl_2**	**10 mol% $Yb(OTf)_3 + H_2O$**	**10 kbar, 60 °C, 42 h**	**66**
13	Toluene	5 mol% $Yb(OTf)_3 + H_2O$	10 kbar, 60 °C, 42 h	54
14	CH_2Cl_2	5 mol% $PhB(OH)_2$	10 kbar, 60 °C, 42 h	57
15	CH_2Cl_2	10 mol% $PhB(OH)_2$	10 kbar, 60 °C, 42 h	61
16	CH_2Cl_2	5 mol% $Eu(fod)_3$	10 kbar, 60 °C, 42 h	41
17	CH_3CN	5 mol% LiOTf	10 kbar, 60 °C, 42 h	24
18	CH_3CN	5 mol% LiOTf + H_2O	10 kbar, 60 °C, 42 h	30
19	CH_2Cl_2	1 mol% p-TsOH • H_2O	10 kbar, 60 °C, 42 h	4

[a] Stoichiometric amounts of the starting materials were used for all reactions. [b] Isolated yields after purification by preparative TLC or column chromatography. [c] See ref. 1. [d] No product formation due to the considerable decomposition of the substrates.

With these results in hand, we then proceeded with the total synthesis of diolmycin A2 (**12**), an anticoccidial agent isolated from a fermentation broth of *Streptomyces* sp. WK-2955 by Professor Omura and his coworkers.[6] Similarly as reported by these authors,[6d] our synthetic route to **1** using epoxide opening reaction with indole as a key step is shown in Scheme 1.[9]



Scheme 1

The required epoxyalcohol intermediate **10** was successfully assembled from monotosylate **4**, readily available from L-tartaric acid, by taking advantage of our own protocol using triflate coupling reactions.[10] Thus, triflation of **4**[11] followed by treatment with 1.2 equiv. of the Grignard reagent **6** in the presence of 0.2 equiv. of CuBr produced cleanly tosylate **8**, mp 84.5-85.0 °C, in 75% yield. Alternatively, the same compound was also prepared from **4** by the action of an excess of **6** followed by tosylation although the yield was low (28%). Exposure of **8** to 60% $HClO_4$ in aqueous CH_3CN gave diol **9** which was immediately treated with K_2CO_3 in abs. MeOH to afford the epoxyalcohol **10**, mp 68.0-69.0 °C, in 88% yield. Then, a solution of **10** and 1.5 equiv. of indole (**1**) in CH_2Cl_2 containing 5 mol% of $Yb(OTf)_3$ and 5 mol% of water was subjected to the above-mentioned process: at 10 kbar and 60 °C for 42 h, the desired adduct **11**, mp 128.0-128.5 °C, was obtained in 51% yield.[7, 12] Finally, catalytic debenzylation of **11** (H_2, 20% Degussa $Pd(OH)_2/C$ in EtOH) provided (*S,S*)-diolmycin A2 (**12**)[13] quantitatively as a highly viscous oil. Spectral data (400 MHz ^1H and 100 MHz ^{13}C NMR) of this sample were identical to those reported for the natural substance.[6a, 14] The absolute configuration of the major component of the natural product {lit.[6b] $[\alpha]_D^{25}$ -12.0° (c 0.1, MeOH)} having (*R,R*)-configuration was thus deduced from the sign of its specific rotation.[14]

In conclusion, we have succeeded in developing a novel method for the epoxide opening reaction with indole under Yb(III)-catalyzed high pressure conditions. As an application of this technique, an expeditious synthesis of (+)-diolmycin A2 in an enantiomerically pure form has been established: a 6-step sequence from monotosylate **4** in 34% overall yield.

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7. Freshly dried solvents were used for all reactions. The unreacted indole was cleanly recovered, while the starting epoxide was completely decomposed under these conditions.
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12. The considerable improvement in this step is particularly noteworthy: for example, the reported method using $SnCl_4$ as a Lewis acid gave only 32% yield.[6d]
13. **12**: FTIR (neat) ν 3411, 1615, 1514, and 1456 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 2.71 (1H, dd, J= 13.7, 8.0 Hz), 2.79 (1H, dd, J = 13.7, 5.6 Hz), 2.91 (1H, dd, J = 14.4, 7.6 Hz), 3.06 (1H, dd, J = 14.4, 6.1 Hz), 3.67 (1H, ddd, J = 8.0, 5.6, 2.5 Hz), 3.80 (1H, ddd, J = 7.6, 6.1, 2.5 Hz), 6.66 (2H, d, J = 8.7 Hz), 6.95 (1H, dd, J = 7.9, 7.0 Hz), 6.98 (2H, J = 8.7 Hz), 7.03 (1H, s), 7.05 (1H, dd, J = 8.0, 7.0 Hz), 7.30 (1H, d, J = 8.0 Hz), 7.47 (1H, d, J = 7.9 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 30.53, 40.11, 73.94, 75.31, 112.08, 112.77, 115.99 (×2), 119.45 (×2), 122.13, 124.08, 128.99, 131.33 (×3), 138.04, 156.53. HRMS, calcd for $C_{18}H_{19}NO_3$: 297.1365; found: 297.1362.
14. We wish to thank Prof. S. Omura of the Kitasato Institute for sending us the spectral data (^1H and ^{13}C NMR) of an authentic sample and information on the optical purity of the natural substance.

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