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N,*N*-Diethyl-(*R*)-[3-(2-aminopropyl)-1*H*-indol-7-yloxy]acetamide: Its Process Chemistry Ranging from Enantiocontrolled Construction of the Chiral Amine Side Chain to Regioselective Functionalization of the Aromatic Starting Materials

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Abstract:

To access *N*,*N*-diethyl-(*R*)-[3-(2-aminopropyl)-1*H*-indol-7-yloxy]acetamide (3), a key intermediate for AJ-9677 (2) acting as a potent and selective agonist for β_3-adrenergic receptors, the (*R*)-configured 2-aminopropyl side chain of 3 is elaborated in three distinct ways: (1) chiral pool synthesis featuring the C-3 acylation of 7-benzyloxy-1*H*-indole (4a) with *N*-(9-fluorenylmethoxycarbonyl)-D-alanyl chloride (6); (2) resolution of (±)-3-(2-aminopropyl)-7-benzyloxy-1*H*-indole (8) via diastereomeric salt formation with *O*,*O*-di-*p*-toluoyl L-(2*R*,3*R*)-tartaric acid (21) to obtain (*R*)-8; and (3) crystallization-induced dynamic resolution (CIDR) by entrainment which transforms *N*,*N*-diethyl-(±)-[3-(*N*-phthaloyl-2-aminopropanoyl)-1*H*-indol-7-yloxy]acetamide (26) entirely into (*R*)-26. As regards 4a and 7-hydroxy-1*H*-indole (4b), the molecular scaffolds on which the above-mentioned chiral maneuvers are being executed, their synthetic approaches are explored threefold: (1) indole-ring construction on 3-benzyloxy-2-nitrotoluene [28; prepared from *m*-cresol (31)] by the modified Leimgruber−Batcho method; (2) direct microbial hydroxylation of indole (34) at its C-7 position; and (3) indirect hydroxylation of indoline (35) at its C-7 position via a $K_2S_2O_8$-mediated Baeyer−Villiger oxidation of the tricyclic product arising from the intramolecular Friedel−Crafts acylation of *N*-succinyl indoline (36).

Introduction

When β_3-adrenergic receptors on the surface of white and brown adipocytes are stimulated by their endogenous agonist, adrenaline (**1**), then lipolysis (fat degradation) and thermogenesis (energy expenditure) are triggered, respectively (Figure 1).[1] Being a potent selective agonist for β_3-adrenergic receptors, {3-[(2*R*)-2-[[(2*R*)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-1*H*-indol-7-yloxy}acetic acid, AJ-9677 (**2**),[2] had been nominated as a clinical candidate to treat obesity,[1] a metabolic syndrome[3] that is often associated with non-insulin dependent (Type-II) diabetes (Figure 1).[4] Hence, synthetic routes were explored intensively to pave a scalable way for *N*,*N*-diethyl-(*R*)-[3-(2-aminopropyl)-1*H*-indol-7-yloxy]acetamide (**3**), a more elaborate half of the two that were to be joined in the convergent synthesis of **2** (Figure 1).[5]

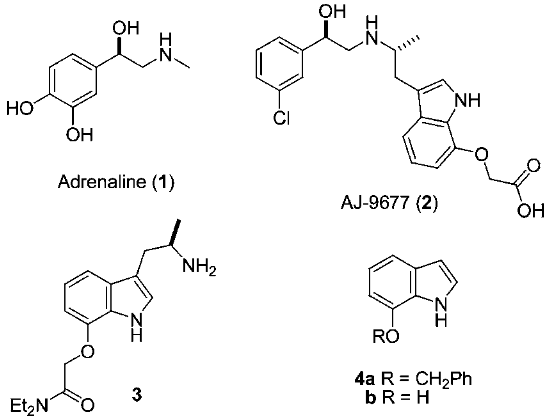

Figure 1. **Structures of adrenaline (1), AJ-9677 (2), its advanced chiral intermediate (3), and indole precursors (4) to 3.**

Thus, this minireview will shed light on the scalable synthesis of (*R*)-**3** in a retrospective direction,[6−8] tracing it back to an ultimate industrial starting point, *m*-cresol (**31**), by way of 7-benzyloxy-1*H*-indole (**4a**) (Figure 1).[9] It will

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(1) Rawls, R. L. *Chem. Eng. News* **1999**, *77* (Jun 21), 35.

(2) (a) Harada, H.; Hirokawa, Y.; Suzuki, K.; Hiyama, Y.; Oue, M.; Kawashima, H.; Yoshida, N.; Furutani, Y.; Kato, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1301.(b) Harada, H.; Hirokawa, Y.; Suzuki, K.; Hiyama, Y.; Oue, M.; Kawashima, H.; Kato, H.; Yoshida, N.; Furutani, Y.; Kato, S. *Chem. Pharm. Bull.* **2005**, *53*, 184.

(3) Rouhi, A. M. *Chem. Eng. News* **2004**, *82* (Nov 22), 83.

(4) For the latest drug therapy for diabetes, see: Dalton, L. W. *Chem. Eng. News* **2004**, *82* (Oct 25), 59.

(5) In its discovery synthesis, AJ-9677 (**2**) was elaborated in a linear fashion as described in ref 2.

(6) Harada, H.; Fujii, A.; Odai, O.; Kato, S. *Org. Process Res. Dev.* **2004**, *8*, 238.

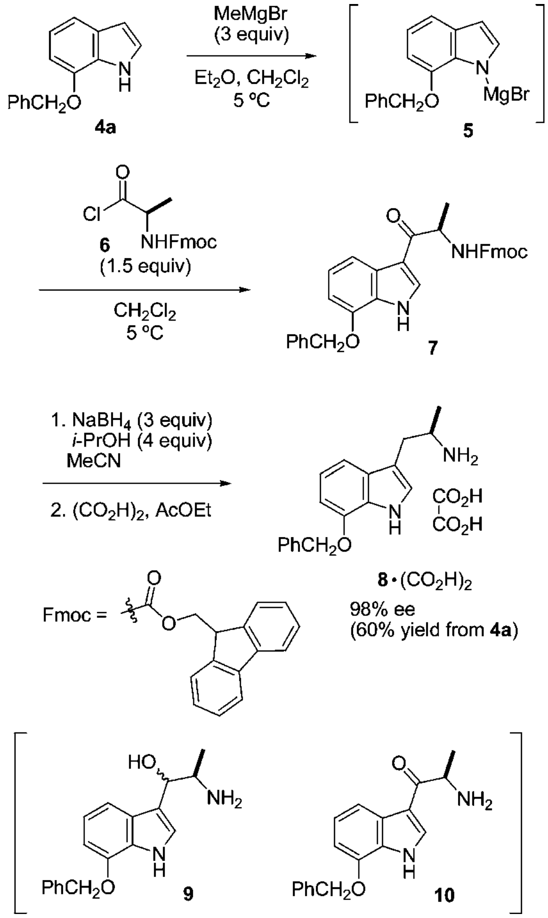
(7) Fujii, A.; Fujima, Y.; Harada, H.; Ikunaka, M.; Inoue, T.; Kato, S.; Matsuyama, K. *Tetrahedron: Asymmetry* **2001**, *12*, 3235.

(8) Murakami, Y.; Ikeda, T.; Inagaki, T. (Beta-Chem, Inc. and Katayama Seiyakusho Co., Ltd.). *Jpn. Kokai Tokkyo Koho* 2005-281,237, 2005.

(9) Harada, H.; Fujii, A.; Kato, S. *Synth. Commun.* **2003**, *33*, 507.

10.1021/op060210h CCC: $37.00

Scheme 1. **Synthesis of the oxalate salt of (*R*)-8 by acylating 4a with *N*-Fmoc-D-alanyl chloride (6)**



then be followed by a brief discussion on newly explored alternative methods to access 7-hydroxy-1*H*-indole (**4b**).[10−12]

Chiral Pool Synthesis of (*R*)-3 by Acylation of 4a with *N*-Fmoc D-Alanyl Chloride (6). To build the stereogenic center of the 2-aminopropyl side chain in (*R*)-**3**, the chirality of D-alanine[13] was used to advantage (Scheme 1).[6] To a 0.5 M solution of **4a** in CH_2Cl_2 was added MeMgBr (3.0 equiv; 3.0 M solution in Et_2O) at 5 °C to give rise to *N*-(bromomagnesio)indole (**5**), which was then reacted with *N*-(9-fluorenylmethoxycarbonyl)-D-alanyl chloride (**6**) (1.5 equiv; 0.375 M solution in CH_2Cl_2) at 5 °C to afford 3-acylindole (**7**). On aqueous workup, crude **7** was obtained as an amorphous solid and was carried forward to the next step without further purification while it was contaminated with unconsumed **4a** and surplus **6**.

Besides **6**, D-alanyl chlorides with different *N*-protection, such as benzyloxycarbonyl, phthaloyl, and trifluoroacetyl, were tested for yield of the acylation and for facilitation in the ensuing reductive removal of the ketonic oxygen from the corresponding 3-acylindole products. However, none of them exceeded **6** in both criteria defined above. As regards the acylation of **4a** with **6**, the following three reaction parameters were examined in combination for a maximum yield of **7**: (1) solvent species for a solution of MeMgBr, THF, PhMe/THF (3:1), and Et_2O; (2) solvent species for the acylation reaction, THF, PhMe, CH_2Cl_2, $CHCl_3$, and Et_2O; and (3) halide species for MeMgX in solution, X = Cl (THF), Br (Et_2O), and I (Et_2O). After experimental comparison, the best conditions for the acylation in question proved to be the use of CH_2Cl_2 (0.5 M for **4a**) as the reaction medium and an ethereal solution of MeMgBr (3.0 M), as described above.

To remove the ketonic oxygen from crude **7**, it was treated with $NaBH_4$ (3.0 equiv) in MeCN (ca. 2.5 v/w) in the presence of *i*-PrOH (4.0 equiv) at reflux for 5 h. Quenching the reaction with MeOH delivered crude (*R*)-3-(2-aminopropyl)-7-benzyloxy-1*H*-indole (**8**), a deoxygenated product from which the *N*-Fmoc protection had been eliminated. It was taken up in AcOEt, and oxalic acid (1.0 equiv) was added to the AcOEt solution to allow the oxalate salt of **8** to be precipitated selectively; filtration afforded **8**•$(CO_2H)_2$ of 98% ee in 60% overall yield from **4a**.

The reductive conversion of **7** to **8** with the concomitant removal of the *N*-Fmoc protection in **7** was also attempted using reducing agents other than $NaBH_4$. For instance, when **7** was treated with BH_3 (2 equiv) in THF at reflux for a day, an alcoholic product without the *N*-protection, 3-[(2*R*)-(2-amino-1-hydroxy)propyl]-7-benzyloxy-1*H*-indole (**9**), was formed along with the desired **8**. Furthermore, when **7** was exposed to vitride {$Na[AlH_2(OCH_2CH_2OMe)_2]$ in a PhMe solution, 4 equiv} in THF (20 v/w) for 5 h, a lot of byproducts were formed besides **8**. In contrast, reduction of **7** with $NaBH_4$ (10 equiv) in refluxing *i*-PrOH for 4 h provided **8** as a solid powder in 36% isolated yield without recourse to chromatographic purification.

On the basis of these preliminary results, the $NaBH_4$-mediated reduction of **7** was further explored in a nonprotic solvent in the presence of a minimum amount of *i*-PrOH to effect the reduction in question with the least possible amounts of $NaBH_4$, since it is known to tend to decompose in protic solvents, such as *i*-PrOH. After experimentation, MeCN was identified as the nonprotic solvent of choice: When **7** was reduced with $NaBH_4$ (3 equiv) in MeCN (5 v/w) in the presence of *i*-PrOH (4 equiv) at reflux for 5 h, a mixture of **8**, **9**, and (*R*)-3-(2-aminopropanoyl)-7-benzyloxy-1*H*-indole (**10**; resulting from **7** with removal of the *N*-Fmoc protection) was produced in a ratio of 85:6:2. From this mixture, **8** could be isolated as its oxalate salt [**8**•$(CO_2H)_2$] in 61% yield. Eventually, further optimization led to identification of those conditions that allowed **4a** to be converted to **8**•$(CO_2H)_2$ of 98% ee in 60% overall yield without isolation of intermediate **7**, as mentioned above.

To protect the primary amine of **8** as *tert*-butyl carbamate, the oxalate salt of **8** was treated with $(Boc)_2O$ (1.0 equiv) in AcOEt (5.0 v/w) in the presence of an aqueous solution of K_2CO_3 (0.4 M, 1.48 equiv) at 5 °C (Scheme 2). Crystalliza-

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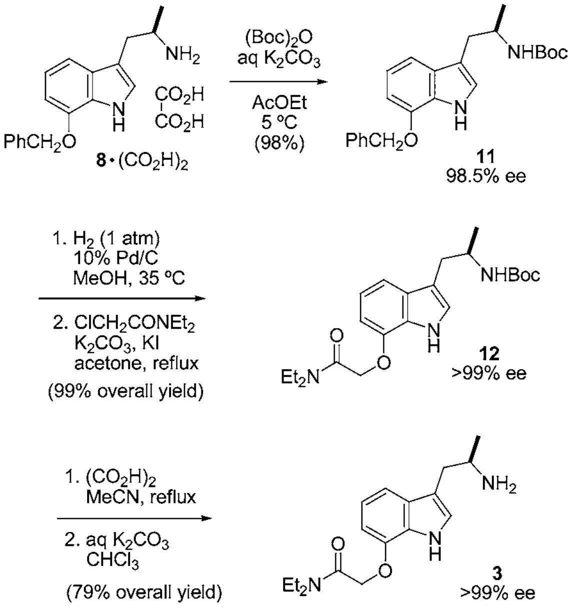
(10) (a) Watanabe, H.; Aritoku, Y.; Hirosue, S.; Fujii, T.; Uematsu, H.; Issiki, K.; Yoshioka, T. (Mercian Corporation). *Jpn. Kokai Tokkyo Koho* 2001-95,577, 2001. (b) Sugimori, D.; Sekiguchi, T.; Hasumi, F.; Kubo, M.; Shirasaka, N.; Ikunaka, M. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 1167.

(11) Ishiyama, K.; Yamada, Y. *Tetrahedron Lett.* **2005**, *46*, 1021.

(12) This review article is based in part on the lecture entitled "Two Case Studies on Process Development with Resolution via Diastereomeric Salt Formation: Their Chronological and Multifaceted Description to Identify the Real Competitiveness" which was given by M.I. at The 2005 Winter Symposium of the Japanese Society for Process Chemistry, Osaka, December 8, 2005.

(13) For the production of D-Ala, see: Ikunaka, M. *chimica oggi/Chemistry Today* **2005**, *23*, 58.

Scheme 2. **Conversion of (*R*)-8·(CO_2H)$_2$ to (*R*)-3 via *N,O*-functional group manipulations**

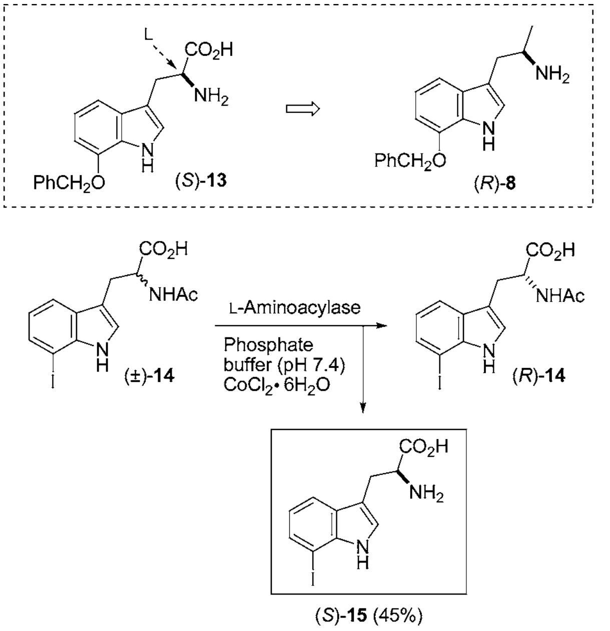


tion from *n*-hexane [3.0 v/w relative to **8**·(CO_2H)$_2$] afforded (*R*)-3-[2-(*N*-*tert*-butoxycarbonyl)aminopropyl]-1*H*-indole (**11**) of 98.5% ee in 98% yield. The *O*-benzyl group was removed from **11** by catalytic hydrogenolysis [H_2, 1 atm; 10% Pd/C, 3% w/w; MeOH, 5 v/w; 35 °C], and the liberated phenolic function was subjected to the *O*-alkylation with *N,N*-diethylchloroacetamide (1.2 equiv) in the presence of K_2CO_3 (1.2 equiv) and KI (5.25 mol %) in refluxing acetone (6.0 v/w) for 5 h. On aqueous workup followed by trituration with AcOEt/*n*-hexane (1:3; 4.0 v/w relative to **11**), *N,N*-diethyl-(*R*)-[3-(2-(*N*-*tert*-butoxycarbonyl)aminopropyl)-1*H*-indol-7-yloxy]acetamide (**12**) of >99% ee was obtained as white crystals in 99% overall yield from **11**.

Finally, **12** was treated with oxalic acid (2.9 equiv) in refluxing MeCN (6.0 v/w) for 4 h to deprotect its *N*-Boc group. When the reaction mixture was allowed to cool to 5 °C, (*R*)-amine (**3**) was precipitated as its oxalate salt. The solid was collected by filtration, and it was added to a mixture of 10% aqueous solution of K_2CO_3 (4.2 v/w relative to **12**) and $CHCl_3$ (10.1 v/w relative to **12**) to liberate the free base. Eventually, trituration with *i*-Pr_2O furnished (*R*)-**3** as white crystals in >99% ee and 79% overall yield from **12**.

Indeed, the enantioselective method to build the chiral side chain in (*R*)-**8** by appending *N*-Fmoc-D-alanyl chloride (**6**) to **4a** is concise, racemization-free, and hence scalable, while it requires the use of environmentally demanding CH_2Cl_2 and flammable, easy-to-ignite Et_2O, though. However, what detracts from this chiral pool approach to (*R*)-**8** is its less efficient atom economy due to the indispensable use of the bulky Fmoc protection; in fact, as many as 15 carbon atoms are lost when (*R*)-**8** of $C_{18}H_{20}N_2O$ (280.16) is assembled from 7-benzyloxy-1*H*-indole (**4a**) of $C_{15}H_{13}NO$ (223.27) and *N*-Fmoc-D-alanyl chloride (**6**) of $C_{18}H_{18}ClNO_3$ (327.78). Thus, to overcome this latent but critical drawback affecting real practicality, other synthetic methods to access (*R*)-**8** were explored as discussed below.

Scheme 3. **Kinetic resolution of *N*-acetyl (±)-7-iodotryptophan (14) by L-aminoacylase**



Resolution of (±)-Amine (8) into its (*R*)-Isomer via Diastereomeric Salt Formation with L-(*R,R*)-DTTA (21). It was envisioned that (*S*)-L-7-benzyloxytryptophan (**13**) might serve as a chiral intermediate in accessing (*R*)-amine (**8**). This is because (*S*)-**13**, possessing the same L-configuration as that of natural proteogenic α-amino acids, should be prepared by enantioselective hydrolysis of *N*-acetyl-(±)-7-benzyloxytryptophan under the influence of readily available L-amino acylase of fungal *Aspegillus* origin. In fact, such a chemoenzymatic approach was assumed to be highly probable as supported by the recent literature reporting kinetic resolution of *N*-acetyl-(±)-7-iodotryptophan (**14**) (Scheme 3):[14] When (±)-(**14**) was treated with L-amino acylase (0.32 w/w) in phosphate buffer (pH 7.4, 127 v/w) in the presence of $CoCl_2$·$6H_2O$ (0.10 w/w relative to the L-amino acylase) at 37 °C, (*S*)-**14** underwent selective hydrolysis, with antipodal (*R*)-**14** being unaffected. After being shaken for 24 h, the reaction was quenched by acidification to pH 5 with a 1 M aqueous solution of HCl. Finally, column chromatography (SEPABEDAS SP207; eluted with H_2O followed by MeOH) provided (*S*)-7-iodotryptophan (**15**) as a white powder in 45% yield.

However, further investigation along this line has remained unexplored because of the lengthy reductive functional group manipulations required for the conversion of the carboxylic acid of (*S*)-**13** to a terminal methyl group of (*R*)-**8**. Under these circumstances, resolution via diastereomeric salt formation did emerge as a more practical option for the chiral separation of (*R*)-**8** from (±)-**8**.

The starting point for the synthesis of (±)-**8** was formylation of **4a** under the Vilsmeir conditions (Scheme 4).[7] When **4a** was treated with $POCl_3$ (1.1 equiv) in DMF (2.75 w/w) at temperatures ≤35 °C, 7-benzyloxy-1*H*-indole-3-carbaldehyde (**16**) was obtained in 99% yield as a crystalline solid

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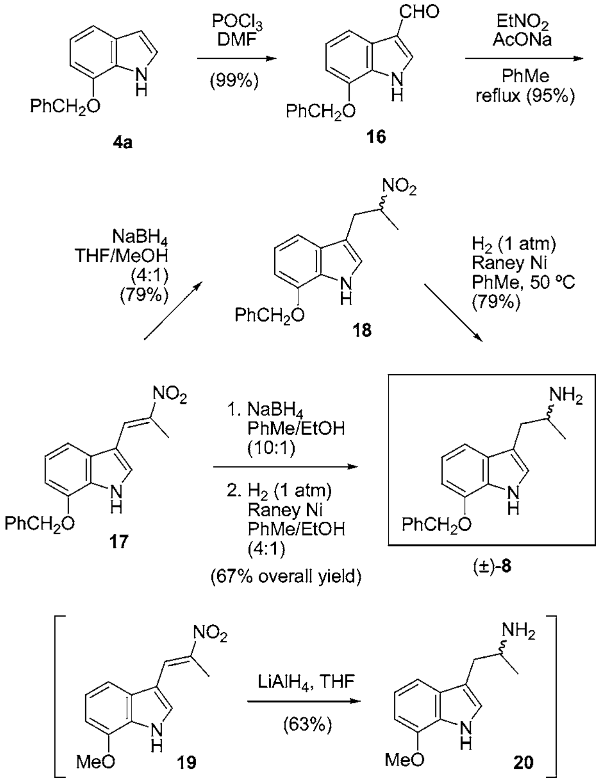
(14) Yamada, Y.; Arima, S.; Okada, C.; Akiba, A.; Kai, T.; Harigaya, Y. *Chem. Pharm Bull.* **2006**, *54*, 788.

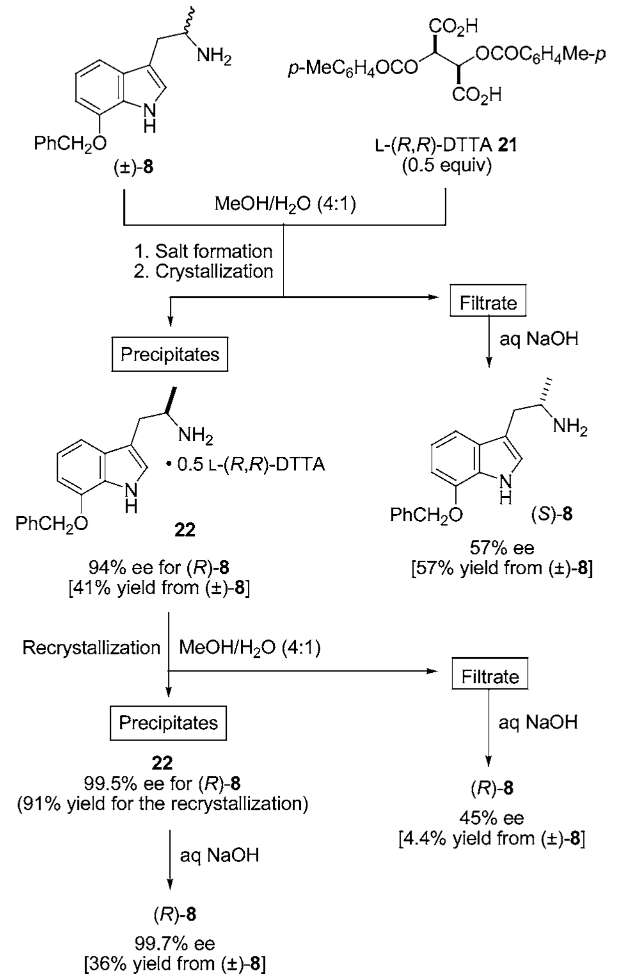
Scheme 4. **Preparation of (±)-amine (8) via two-step reduction of (±)-nitroolefin (17)**



on aqueous quenching. A mixture of **16**, EtNO$_2$ (3.0 equiv), AcONH$_4$ (0.5 equiv), and PhMe (4.4 v/w) was heated at reflux for 3 h to promote nitroaldol reaction, and the reaction was driven to completion by dehydration via azeotropical removal of the generated water. On cooling the reaction mixture to temperatures between 0−5 °C, nitroolefin (**17**) was precipitated and isolated in 95% yield as a crystalline solid.

With 1-(7-methoxy-1*H*-indol-3-yl)-2-nitropropene (**19**), its LiAlH$_4$-reduction in THF provided saturated primary (±)-amine (**20**) in 63% yield,[15] with LiAlH$_4$ fulfilling the following two tasks in sequence: (1) saturation of the electron-deficient olefin in **19** by conjugate addition of a hydride; and (2) reductive deoxygenation of the resulting aliphatic nitro group to a primary amine function in (±)-**20** (Scheme 4). Thus, to avoid the use of expensive pyrophoric LiAlH$_4$, reductive conversion of **17** to (±)-**8** was explored in a stepwise manner, which culminated in the following two-step procedures:[7] First, **17** was treated with NaBH$_4$ (1.0 equiv) in PhMe/MeOH (6:1; 4.5 v/w) with heating at 40 °C for 1 h to give nitroalkane (**18**) in 79% yield as a crystalline solid after recrystallization from PhMe/MeOH (10:3; 8.4 v/w relative to **17**). Then, the nitro group of **18** was subjected to catalytic hydrogenation (Raney Ni, 0.32 v/w; washed with MeOH and PhMe prior to use; H$_2$, 1 atm; 49−50 °C; 13 h) to afford (±)-**8** in 79% yield as a crystalline solid on trituration with AcOEt (1.6 v/w relative to **18**), its overall yield from **17** being 63%. Under these catalytic reduction conditions, no hydrogenolytic cleavage was observed with the *O*-benzyl protection in **18**.

Scheme 5. **Resolution of (±)-amine (8) into its (*R*)-isomer via diastereomeric salt formation with L-(*R*,*R*)-DTTA (21)**



The procedures thus developed for the stepwise reduction of **17** to (±)-**8** were streamlined to allow each reduction to proceed in a binary medium of the same solvent species, PhMe and EtOH, and thereby to dispense with isolation of the intermediate **18**.[12] Under the optimized conditions, the NaBH$_4$-mediated conjugate delivery of a hydride was conducted in PhMe/EtOH (10:1). After the boron-derived inorganic materials were removed by aqueous workup, the PhMe/EtOH ratio of the solution containing crude **18** was adjusted to 4:1. The solution was then exposed to hydrogen (1 atm) in the presence of Raney Ni catalyst to give (±)-**8** in 67% overall yield from **17**; the quality of (±)-**8** thus obtained proved to be the same as that prepared by the previous method in which **18** had been isolated as a solid.

To effect the resolution via diastereomeric salt formation, (±)-amine (**8**) was combined with *O*,*O*-di-*p*-toluoyl L-(2*R*,3*R*)-tartaric acid [L-(*R*,*R*)-DTTA (**21**); 0.5 equiv relative to (±)-**8**] in MeOH/H$_2$O (4:1; 8.53 v/w) with heating at 70 °C (Scheme 5). The resulting homogeneous mixture was allowed to cool to 49 °C. It was then seeded with a few crystals of diastereomeric salt (**22**) [L-(*R*,*R*)-DTTA (**21**)/(*R*)-**8** of 95.5% ee (0.5 :1.0)] to induce crystallization.[7] After the mixture was cooled to temperatures between 15 and 17 °C, the precipitated solid was collected by filtration to give diastereomeric salt (**22**) [(*R*)-**8**•0.5 L-(*R*,*R*)-DTTA (**21**)] in 41% yield

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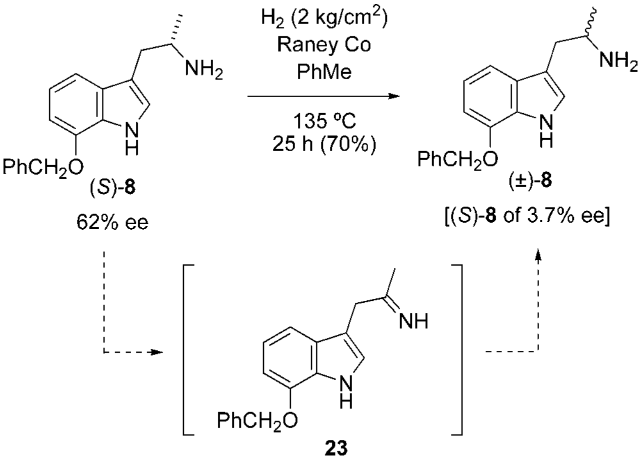
(15) Kalir, A.; Balderman, D.; Edery, H.; Porath, G. *Isr. J. Chem.* **1967**, *5*, 129.

Scheme 6. **Racemization of the off-enantiomer [(*S*)-8] over Raney Co under hydrogen**



from (±)-**8**; the enantiomeric purity of (*R*)-**8** contained in this salt was 94% ee. The filtrate was concentrated to remove MeOH, and the resulting syrupy residue was treated with an aqueous solution of NaOH (45% w/w) to break the salt. The freed base was then triturated with AcOEt to give antipodal (*S*)-**8** of 57% ee as a solid in 57% yield from (±)-**8**.

The diastereomeric salt (**22**) containing (*R*)-**8** of 94% ee was dissolved in MeOH/H_2O (4:1; 10 v/w) by heating to 65 °C. The solution was cooled to 58 °C, and it was seeded with a few crystals of **22** containing (*R*)-**8** of 99.0% ee. The mixture was allowed to cool to room temperature and left to stand overnight. On filtration, recrystallized salt (**22**) was obtained in 91% yield, with the enantiomeric purity of (*R*)-**8** contained in it being elevated to 99.5% ee. The filtrate was concentrated to remove MeOH. To the aqueous residue was added an aqueous solution of NaOH (45% w/w) to liberate the free amine; trituration with AcOEt provided (*R*)-**8** of 45% ee as a solid in 4.4% yield from (±)-**8**.

The recrystallized salt (**22**) containing (*R*)-**8** of 99.5% ee was suspended in H_2O (5.0 v/w), and an aqueous solution of NaOH (45% w/w, 2.2 equiv) was added to break the salt; the freed base [(*R*)-**8**] precipitated spontaneously from the aqueous mixture at room temperature. Finally, filtration provided (*R*)-**8** of 99.7% ee as a solid in 36% overall yield from (±)-**8**.

The resolution process thus developed would still remain less practical unless the off-enantiomer [(*S*)-**8**] could be reused for another round of the resolution.[16] Hence, its racemization was investigated, and the conditions for this salvage operation were established, which can be illustrated as follows (Scheme 6):[7] A solution of (*S*)-**8** (62% ee) in PhMe (80 v/w) was heated to 135 °C under an atmosphere of H_2 (2 kg/cm^2) in the presence of Raney Co [1.0 w/w; washed with H_2O (6.0 v/v; ×2), MeOH (6.0 v/v; ×3), *i*-PrOH (6.0 v/v; ×2), and PhMe (6.0 v/v; ×5) prior to use]. The heating was continued for 25 h, and then organic materials were separated from insoluble metallic materials. After concentration, the organic solid residue was triturated with AcOEt to afford (*S*)-**8** of 3.7% ee as a colorless solid in 70% yield.[17] The racemization should proceed via dehydrogenation of (*S*)-enriched **8** to imine (**23**) and random hydrogenation of **23**, both taking place on the surface of the Raney Co catalyst.

Indeed, when the reaction was terminated in 25 h, the racemization was incomplete with the (*S*)/(*R*) ratio in **8** being still 51.85:48.15, as mentioned above. However, such circumstances would cause no serious problem to arise because (±)-**8** can be reconstituted with ease by blending (*S*)-**8** of 3.7% ee (arising from the racemization process) with (*R*)-**8** of 45% ee (recovered from the recrystallization filtrate) in a ratio of 92.4:7.6.

Now that the method to recycle the off-enantiomer [(*S*)-**8**] has been established, (±)-**8** as a whole can be converted to the desired single enantiomer [(*R*)-**8**] in theory. However, if such a transformation can be achieved in one pot, it should compare favorably with the above-discussed resolution processes involving racemization to recycle the off-enantiomer.

Asymmetric Access to *N*-Phthaloyl-(*R*)-aminoketone (26) via Crystallization-Induced Dynamic Resolution (CIDR) by Entrainment. Crystallization-induced dynamic resolution (CIDR) is a process in which both enantiomers of a racemic compound are converted to a desired single enantiomer via its selective crystallization with the concomitant racemization of another in situ.[18] It can be also defined as spontaneous resolution combined with a second-order asymmetric transformation.[19] In the enantioselective synthesis of (*R*)-**3**, an entrainment version of CIDR was developed successfully whereby *N*-phthaloyl-(±)-aminoketone (**26**) was transformed completely into its (*R*)-isomer, as outlined in Scheme 7.[8]

On dissolution of (±)-**26** [prepared by acylation of *N*,*N*-diethyl-(1*H*-indol-7-yloxy)acetamide (**24**) with *N*-phthaloyl-(±)-alanyl chloride (**25**)[20]] in *i*-PrOH (9.0 v/w) with heating, 1,5-diazabicyclo[4.3.0]non-5-nene (DBN; 0.1 w/w) was added.[8] The homogeneous mixture was then seeded with (*R*)-**26** of 100% ee [0.005 w/w relative to (±)-**26**; prepared by the method similar to that depicted in Scheme 1[21]] at 65 °C. The mixture was allowed to cool gradually to 20 °C and precipitated crystalline materials were collected by filtration to give (*R*)-**26** of 99.4% ee in 72.5% yield.

According to a description in the patent application,[8] (*R*)-**26** can be converted to (*R*)-**3** via catalytic hydrogenolysis (H_2, Pd/C, H_2SO_4) to remove the ketonic oxygen from (*R*)-**26** and hydrazinolysis (H_2NNH_2) to deprotect the *N*-phthaloyl group, yet no relevant experimental detail was recorded, though.

Now that the methods to build the 2-amionopropyl side chain of (*R*)-configuration have been discussed to a comprehensive degree, it is high time to turn attention towards

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[16] Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417.

[17] For the racemization of a chiral primary amine over Raney Ni, see: Hirayama, Y.; Ikunaka, M.; Matsumoto, J. *Org. Process Res. Dev.* **2005**, *9*, 30.

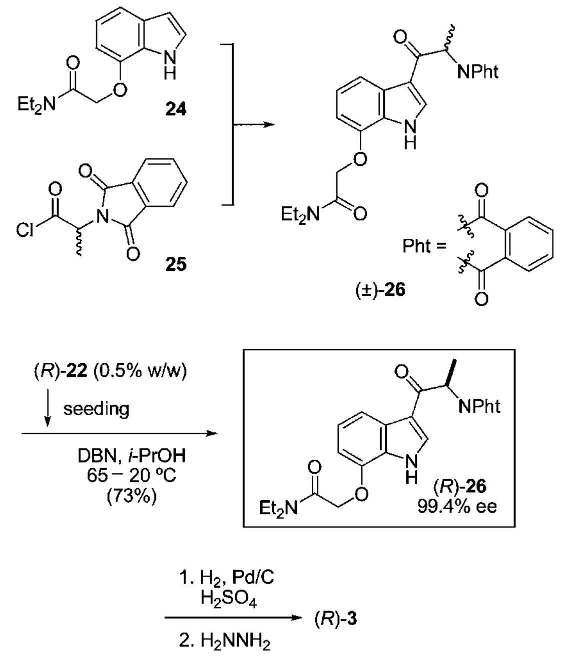
[18] Anderson, N. G. *Org. Process Res. Dev.* **2005**, *9*, 800.

[19] Fogassy, E.; Nógrádi, M.; Pálovics, E.; Schindler, J. *Synthesis* **2005**, 1555.

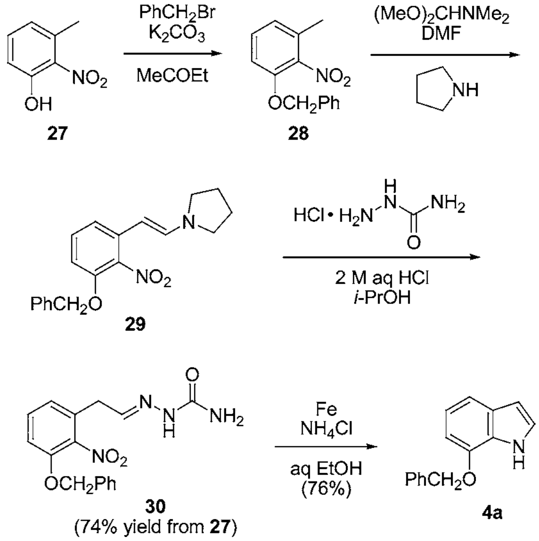
[20] Yamaguchi, T.; Ban, M.; Yanagi, T.; Kikuchi, K.; Kubota, M.; Ozawa, T. (Kissei Pharmaceutical Co., Ltd.). WO 2004/005251.

[21] Kato, S.; Harada, H.; Fujii, A.; Odai, O. (Dainippon Pharmaceutical Co., Ltd.). *Jpn. Kokai Tokkyo Koho* 1999-2,551,743, 1999.

Scheme 7. **Asymmetric transformation of (±)-26 to (*R*)-26 via crystallization-induced dynamic resolution (CIDR) by entrainment**



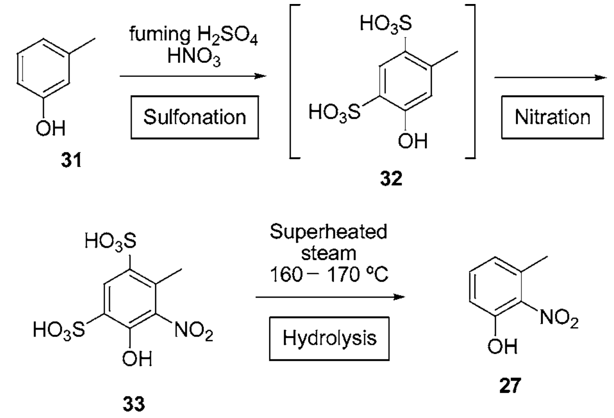
Scheme 8. **Synthesis of 4a from 3-hydroxy-2-nitrotoluene (27) via the modified Leimgruber and Batcho method**



how to secure the 7-oxygenated-1*H*-indole nucleus (**4**), a molecular prerequisite for the side chain elaboration.

Preparation of 7-Benzyloxy-1*H*-indole (4a). To access **4a** with a benzyloxy group at its C-7 position, the Leimgruber and Batcho method[22] was applied to 3-hydroxy-2-nitrotoluene (**27**) with modification (Scheme 8);[9,23] vide infra for the preparation of this nominal starting material (**27**). When **27** was exposed to $PhCH_2Br$ (1.0 equiv) in the presence of K_2CO_3 (1.0 equiv) in refluxing MeCOEt (9.8 v/w) for 4 h, *O*-benzylation proceeded without incident. On the usual aqueous workup, crude benzyl ether (**28**) was obtained as a pale yellow oil, which was employed in the next step without further purification.

Scheme 9. **Preparation of 27 from *m*-cresol (31)**



Crude *o*-nitrotoluene (**28**) thus prepared was next treated with pyrrolidine (2.0 equiv) and DMF dimethyl acetal [$(MeO)_2CHNMe_2$; 2.0 equiv] in refluxing DMF (3.1 v/w) for 5 h to yield one-carbon-homologated enamine (**29**). The reaction mixture containing **29** was cooled to 5 °C and diluted with *i*-Pr_2O (3.1 v/w relative to **28**). A few crystals of semicarbazone (**30**) were added to the mixture, and a solution of semicarabazide hydrochloride ($H_2NCONHNH_2{\cdot}HCl$; 1.2 equiv relative to **28**) in a 2 M aqueous HCl solution (11.1 v/w relative to **28**) was added in one portion at temperatures between 7 and 35 °C.[24] To the mixture was then added a two-phase mixture of *i*-Pr_2O/H_2O (1:1; 2.1 v/w relative to **28**) at room temperature. Finally, the precipitated solid was collected by filtration to give 3-benzyloxy-2-nitrophenylacetaldehyde semicarbazone (**30**) as pale yellow crystals in 74% overall yield from **27**.

When **30** was subjected to Fe-mediated reduction [Fe, 3.9 equiv; NH_4Cl, 2.1 equiv; $EtOH/H_2O$ (2:1), 18.2 v/w; refluxing; 1 h], the resulting aniline underwent spontaneous cyclization to an indole system to deliver **4a**. After insoluble materials were filtered off, the filtrate was worked up in a conventional manner. When a solution of crude **4a** in PhMe/*n*-hexane (1:2; 2.7 v/w relative to **30**) was seeded with a few crystals of **4a**, crystallization took place to give purified **4a** as a brownish solid in 76% yield.

Preparation of Consecutively Trisubstituted Phenol (27). The nominal starting material (**27**) for the Leimgruber and Batcho indole synthesis was, in turn, prepared from *m*-cresol (**31**) as summarized in Scheme 9.[25] To introduce a nitro group to the position flanked by the methyl and hydroxy groups in **31**, two other positions that are as reactive but less congested have to be blocked in advance by sulfonation. To a solution of **31** in fuming H_2SO_4 (6–7% SO_3; 3.7 v/v) was added gradually a mixture of fuming H_2SO_4 (6–7% SO_3; 0.99 v/v) and HNO_3 (*d* 1.5; 0.43 v/v).[25c] Under these controlled conditions, **31** underwent double sulfonation and nitration of the resulting disulfonic acid (**32**) in sequence in 24 h to give 2-nitro-3-methyl-4,5-disulfonylphenol (**33**). After the reaction mixture was diluted with H_2O (4.63 v/v),

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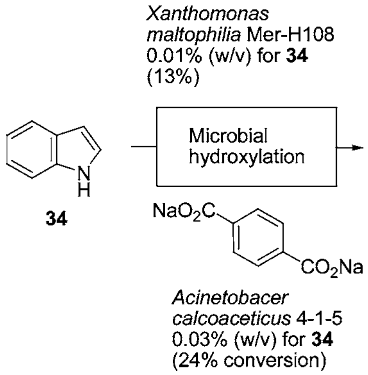
[22] Batcho, A. D.; Leimgruber, W. *Org. Stnth.* **1985**, *63*, 214.

[23] For other relevant approaches, see: Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, *21*, 611.

[24] Kruse, L. I. *Heterocycles* **1981**, *16*, 1119.

[25] (a) Yang, C.-G.; Wang, J.; Jiang, B. *Tetrahedron Lett.* **2002**, *43*, 1063.(b) Sasaki, M.; Nodera, K.; Mukai, K.; Yoshioka, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 276.(c) Gibson, G. P. *J. Chem. Soc.* **1923**, 1269. (d) Ek, A.; Witkop, B. *J. Am. Chem. Soc.* **1954**, *76*, 5579.

Scheme 10. **Microbial hydroxylation of indole (34) at its 7 position**



superheated steam (160−170 °C) was passed through the aqueous mixture to distill **27** out with the steam as the sulfonyl groups were removed from **33** hydrolytically. On extractive workup of the distillate, **27** was isolated as a yellow oil in 80% yield.

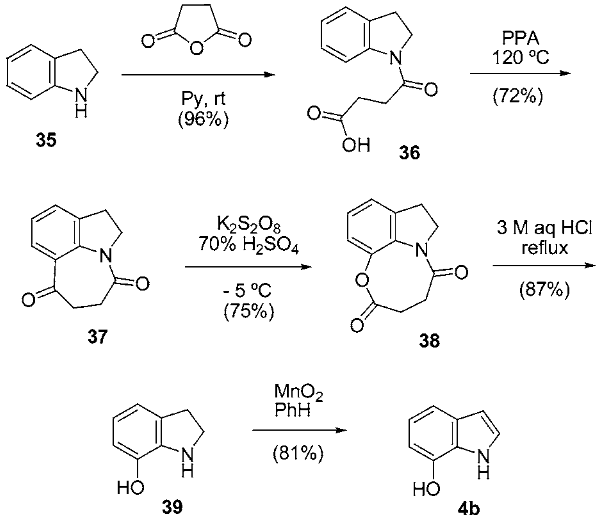
To sum up, it is not impossible to assemble 7-benzyloxy-1*H*-indole (**4a**) from *m*-cresol (**31**) on scale; however, requiring as many as six reactions, such a synthetic task is a demanding one, as can be seen from the above discussion. Thus, exploratory effort was devoted towards developing preparative methods to access 7-hydroxy-1*H*-indole (**4b**) in a more concise manner.

Microbial Hydroxylation of Indole (34) at Its C-7 Position. To introduce a hydroxy group to the C-7 position of indole (**34**) in a single step, microbial hydroxylation was investigated (Scheme 10). When the terrestrial flora of microorganisms was explored for those capable of the C-7 hydroxylation of **34**, *Xanthomonas maltophilia* Mer-H108 was identified as the most competent strain.[10a] However, the hydroxylation in question took place only when *X. maltophilia* Mer-H108 was incubated with **34** at 28 °C for 21 h with its concentrations not being higher than 0.01% w/v; on ion-exchange chromatography, **4b** was obtained as crystals in an isolated yield of 13%.

Directed microbial screening was also conducted by exploring stock cultures of microorganisms able to degrade and grow on disodium terephthalate (DT) since such microorganisms were expected to produce unique hydroxylating enzymes for the DT utilization.[10b] From among 12 stock cultures of DT-utilizing microorganisms, *Acinatobacter calcoaceticus* 4-1-5 was identified as the strain exhibiting the highest hydroxylating activity. However, even under the optimized conditions, incubation of *A. calcoaceticus* 4-1-5 was possible with **34** only at its concentration of 0.03% (w/v) in the presence of DT (0.1% w/v) at 28 °C (w/v): under such dilute conditions, **34** was transformed into **4b** at 24% conversion in 24 h.

In the laboratory, indole (**34**) can be hydroxylated at its C-7 position in a single step using *X. maltophilia* Mer-H108 or *A. calcoaceticus* 4-1-5; however, such microbial hydroxylation is not amenable to scale up due to the poor yield of **4b** and the low volume efficiency. Thus, an alternative chemical method to set up the C-7 hydroxyl group in indole (**34**) was explored.

Scheme 11. **Synthesis of 4b from indoline (35) via intramolecular Friedel−Crafts acylation**



Synthesis of 4b from Indoline (35) via Electrophilic Cyclization. Intramolecular oxy-functionalization of the aromatic position adjacent to the nitrogen atom in indoline (**35**) was conceived to have access to **4b**, and this plan was put into practice successfully as outlined in Scheme 11.[11,26] When **35** was treated with succinic anhydride (1.1 equiv) in Py (19 v/w) at room temperature for 5 h, it underwent *N*-acylation uneventfully to give *ω*-carboxyamide (**36**) as a crystalline solid in 96% yield. Intramolecular Friedel−Crafts acylation was then effected by exposing **36** to polyphosphoric acid (PPA; 20 w/w) at 125 °C for 15 h. On aqueous workup followed by column chromatography [silica gel, 8.0 w/w relative to **36**; eluted with *n*-hexane/AcOEt (4:1)], 1,2,5,6-tetrahydro-azepino[3,2,1-hi]indole-4,7-dione (**37**) was obtained as a solid in 72% yield.

On treatment with potassium peroxodisulfate ($K_2S_2O_8$; 5.0 equiv) in a 70% aqueous solution of H_2SO_4 (12.0 v/w) at −5 °C for 0.5 h,[27] tricyclic ketolactam (**37**) underwent oxygen insertion between the aromatic and ketonic carbons via a Baeyer−Villiger-type reaction. When the reaction was quenched with ice, crystalline materials precipitated spontaneously, which were collected by filtration to give 1,2,8,9-tetrahydro-6-oxa-10a-aza-cycloocta[cd]indene-7,10-dione (**38**) in 75% yield.

Having served its relaying role, the succinic acid residue [$-OC(CH_2)_4CO-$] was removed hydrolytically from amidolactone (**38**): A suspension of **38** in a 3 M aqueous solution of HCl (33.3 v/w) was heated at reflux for 5 h. On aqueous workup, column chromatography [silica gel, 16.7 w/w relative to **38**; eluted with CH_2Cl_2] afforded 7-hydroxyindoline (**39**) as a crystalline solid in 87% yield. Finally, **39** was subjected to MnO_2-mediated oxidative aromatization [MnO_2, 2.0 equiv; PhH, 50 v/w; refluxing; 6 h].[28] After

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(26) For an oxidative version of the cyclative functionalization, see: Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem.* **1997**, *62*, 6582.

(27) Reissenweber, G.; Mangold, D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 222.

(28) For alternative methods for indoline dehydrogenation, see: Tilstam, U.; Weinmann, H. *Org. Process Res. Dev.* **2002**, *6*, 384.

(29) *Handbook of Chiral Chemicals*, 2nd ed.; Ager, D., Ed.; CRC Press: Boca Raton, FL, 2006.

aqueous workup followed by column chromatography [silica gel, 25.0 w/w relative to **38**; eluted with *n*-hexane/AcOEt (4:1)], crystalline **4b** was eventually obtained as a solid in 81% yield.

Summary

From the above discussion on the process development with (*R*)-**3**, one could draw the following concluding remark, which may read somewhat ironical: modern sophisticated methods for chiral synthesis, such as chiral pool synthesis, resolution, and CIDR, should end up fruitless unless achiral or racemic intermediates of elaborate structures are available on which such state-of-the-art synthetic maneuvers are being deployed.[29]

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