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THE IDEAL SYNTHETIC METHOD AIMED AT THE LEADS FOR AN α_2-BLOCKER, AN INHIBITOR OF BLOOD PLATELET AGGREGATION, AND AN ANTI-OSTEOPOROSIS AGENT[1]

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Abstract – According to the definition of the ideal synthetic method, an example aimed at the leads for an α_2-blocker, an inhibitor of platelet aggregation, and an anti-osteoporosis agent is established starting from tryptamine. The originality rate, the intellectual property, and the application potential factors of the method are 71, 54, and 100, respectively. The method employs only conventional reagents and reaction conditions without using any protecting groups.

We have thus far proposed our synthetic philosophy for evaluating the effectiveness of organic synthesis that consists of three measures such as the originality rate (OR),[2a] the intellectual property factor (IPF),[2b] and the application potential factor (APF).[2b] The formulas for calculating OR, IPF, and APF are shown in the reference 3. As evidenced by definition,[2,3] the OR shows a proportion of the number of originally developed steps to that of synthetic steps.[2,3a] The IPF is a total rate of one's own intellectual properties involved in every reaction and every compound in the synthesis.[2,3b] The APF is the sum of application potential of starting material, target compound, and all synthetic intermediates.[2,3c] On the basis of these factors, we have defined a synthetic method having the highest OR, IPF, and APF values as the "ideal synthetic method",[4] in which every synthetic intermediate, including starting material and target

compound, has either a biological activity or useful functionality. The ultimate is the one-step synthesis out of the ideal synthetic methods.

Scheme 1

a) R^1 = COOMe; **b**) R^1 = Ac; **c**) R^1 = an appropriate alkyl and acyl group.

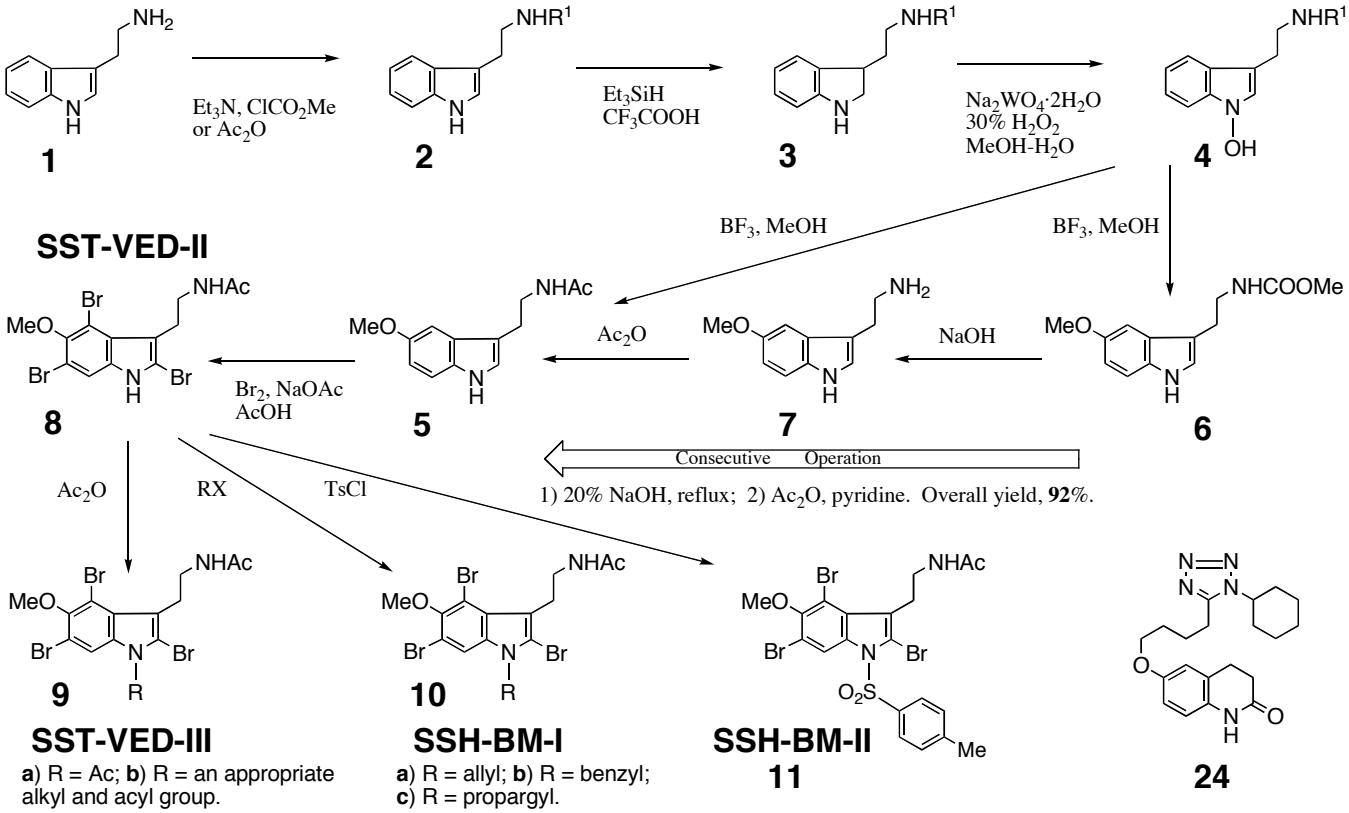
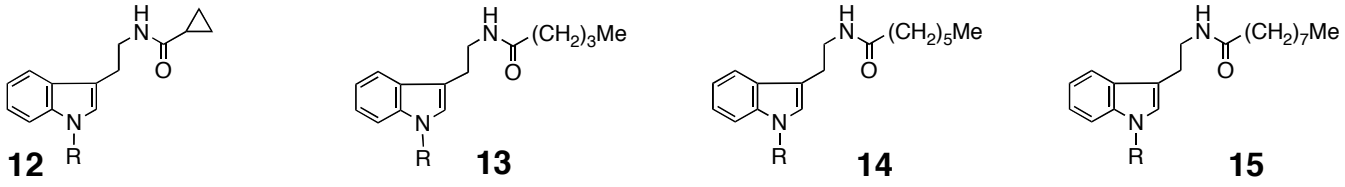


Figure 1

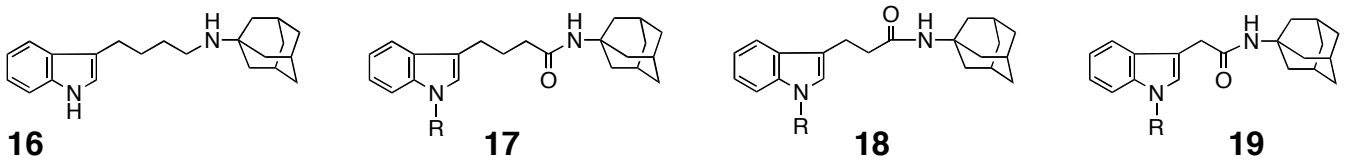


12
a) R = OH: 15.7 ± 6.8%
b) R = H: 21.4%

13
a) R = OH: 25.6 ± 6.0%
b) R = H: 26.9 ± 11.4%

14
a) R = OH: 66.2 ± 13.9%
b) R = H: 70.0 ± 6.9%

15
a) R = OH: 79.0 ± 13%
b) R = H: 80.7 ± 2.5%

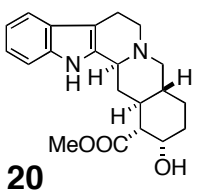


16
91.5 ± 1.3%

17
a) R = OH: 87.7 ± 8.53%
b) R = H: 58.6 ± 10.6%

18
a) R = OH: 17.8%
b) R = H: 60.6 ± 20.7%

19
a) R = OH: 100.0 ± 0.00%
b) R = H: 64.2 ± 8.70%

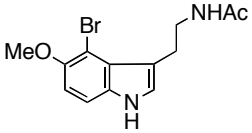


20
yohimbine: 100%

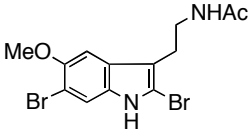
5
6.7 ± 6.7%

8
85.6 ± 12.0%

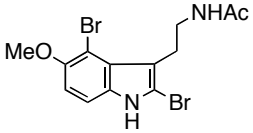
9a
97.6 ± 2.4%



21
20.3 ± 4.6%



22
64.0 ± 4.1%



23
73.5 ± 15.3%

To make our philosophy clearer, we reported a synthesis of 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole as the first concrete example of a six-step near-ideal synthetic method in a previous paper.[2b] As the second example, we have now established more sophisticated six-step near-ideal synthetic method (Scheme 1) with the OR, IPF, and APF values of 71, 54, and 100, respectively, targeting our own intellectual properties for α_2-blockers,[5] inhibitors of platelet aggregation,[6] and anti-osteoporosis agents,[7] starting from biologically active tryptamine (**1**).

The first step is a conventional acylation of **1** with methyl chloroformate or acetic anhydride to give *N*b-methoxycarbonyl- (**2a**) and *N*b-acetyltryptamines (**2b**) in quantitative yields, respectively. Our 1-hydroxyindole synthetic method[8] is employed in the second and the third steps. Reduction was achieved successfully with Et_3SiH in trifluoroacetic acid to provide 2,3-dihydrotryptamines (**3a**,**b**). Subsequent oxidation of **3a**,**b** with $Na_2WO_4{\cdot}2H_2O$ and 30% H_2O_2 in MeOH–H_2O afforded 1-hydroxycompounds (**4a**,**b**) in 63 and 62% overall yields, respectively.

The fourth step is the unprecedented nucleophilic substitution reaction in indole chemistry.[8] Treatment of **4b** with BF_3 in MeOH underwent regioselective methoxylation at the 5-position providing melatonin (**5**) in 85% yield.[9] Similar treatment of **4a** produced **6** in 85% yield. Alkaline hydrolysis of **6** followed by acetylation of the resultant **7** with Ac_2O produced **5** as an alternative synthetic route. These two steps were performed by consecutive operation in 92% overall yield.

Bromination of **5** with Br_2–NaOAc (3 mol eq.) is the fifth step giving a 94% yield of 2,4,6-tribromomelatonin[9] (**8**) that was led to 1-acetyl-2,4,6-tribromomelatonin (**9**) with Ac_2O in a quantitative yield. The sixth step is the treatment of **8** with allyl, benzyl, or propargyl bromides, and tosyl chloride in the presence of K_2CO_3 producing **10a**, **10b**, **10c**, and **11** in 95, 83, 97, and 75% yields, respectively.

We have discovered that **2a** and **2b** are medium, whereas both **8** and **9** are potent leads for α_2-blockers. We named them SST-VED-I, -II, and -III type compounds, respectively. In order to study the structure-activity relationship of SST-VED-I compounds, we prepared various *N*b-substituted tryptamines (**2c, 12—15**) and analogs (**16—19**) as shown in Figure 1. Yohimbine (**20**) is a folk medicine widely used among people as an α_2-blocker to treat erectile dysfunction (ED). When the activity of yohimbine is made a standard for 100, those of **8**, **9a**, **15**, **16**, **17a**, and **19a** are found to be almost equal.[5] In a series of compounds (**12—15**), the activity increases depending on the length of *N*b-acyl side chain.[5] In addition, differences in activities are small between N(1)—OH and N(1)—H compounds. Interestingly, the adamantyl group has a remarkable enhancing effect as demonstrated in typical compounds (**16—19**). As regards brominated melatonins, SST-VED-II compounds (**21—23**, **9a**), the activity becomes stronger as the number of bromine atom increases. Compounds (**9b**) are expected to be potent α_2-blockers as well.

On the other hand, we had discovered that 1-hydroxytryptamines were fundamentally inhibitors of platelet aggregation.[6] 1-Hydroxy-*N*b-methoxycarbonyltryptamine (**4a**: IC_{50} 0.32 μM) is one of the best leads and ten times more potent than cilostazole (**24**: IC_{50} 3.10 μM) and **4b** (IC_{50} 3.10 μM) in the inhibition test on arachidonic acid induced platelet aggregation in rabbit PRP.[6]

We have discovered that 1-alkenyl- (**10a—c**) and 1-tosyl-2,4,6-tribromomelatonins (**11**) stimulate osteoblast activity and suppress osteoclast activity in the cultured scales[10] of goldfish in 10^{-8} mol/L.[7] Thus, we have succeeded in creating potent and promising leads for anti-osteoporosis agents and named them SSH–BM-I and -II type compounds, respectively.

In the above six-step synthesis, every compound has either a biological activity or a useful functionality. The APF value of this synthesis is therefore 100 (100 x 7/7). The IPF value of the synthesis is 54 (100 x 7/13) because **4**, **8**, **9**, **10a—c**, and **11** are our compounds, and three reactions (a set of the second and the third,[8] the fourth,[9] and the fifth[9] steps) are our own reactions or findings. The originality rate[2] of the synthesis is 71 (100 x 5/7). The detailed results of biological evaluations will be reported in due course.

ACKNOWLEDGMENTS

The authors express their cordial gratitude to Dr. K. Kurashina (Kissei Pharmaceutical Ind.) for the evaluations of inhibitory activity of platelet aggregation.

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3. a) The OR is calculated by the following formula.

$$OR = 100 \times \frac{\text{The Number of Newly Developed Steps} + 1}{\text{Total Number of Synthetic Steps} + 1}$$

b) The IPF is figured by the following formula.

$$IPF = 100 \times \frac{\left(\begin{array}{l}\text{The Number of Compound}\\ \text{Having Intellectual Property}\end{array}\right) + \left(\begin{array}{l}\text{The Number of Synthetic Process}\\ \text{Having Intellectual Property}\end{array}\right)}{2 \times (\text{The Number of Synthetic Process}) + 1}$$

c) The APF is obtained by the following formula.

$$APF = 100 \times \frac{\text{The Number of Compound Having either Biological Activity or Other Useful Functionality}}{\text{The Number of Synthetic Process} + 1}$$

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