THE PRACTICAL SYNTHESIS OF DISSYMMETRICAL 1,3,5-TRIOXAZATRIQUINANE DERIVATIVES COMPRISED OF THREE DISTINCT CARBONYL COMPOUNDS

Shigeto Hirayama, Koji Obayashi, Naohisa Wada, Kousuke Ohyama, Shizuho Fuku, Koji Koyano, Fumika Karaki, Kennosuke Itoh, Hiroshi Nagase, and Hideaki Fujii

Abstract – We have previously synthesized various 1,3,5-trioxazatriquinane derivatives consisting of not only three identical carbonyl compounds but also two identical carbonyl moieties as well as another type of carbonyl compound. However, dissymmetrical derivatives prepared from three distinct carbonyl compounds have not yet been selectively synthesized. Herein, we developed a selective synthetic method of such dissymmetrical derivatives: free α-hydroxyaldehydes were slowly added to a solution of protected α-hydroxyaldehydes, ammonium chloride, and sodium acetate to selectively provide key intermediate oxazolines, which were successfully converted into the objective dissymmetrical derivatives.

INTRODUCTION

In the campaign for drug discovery, the emergence in the late 20th century of high throughput screening and combinatorial chemistry techniques enabled the screening of hundreds of thousands of compounds in a short period of time. However, such drug discovery programs did not necessarily provide fruitful results: the successes in the clinical development did not increase. These circumstances lead the medicinal chemistry community to concentrate on the physicochemical properties of the drug candidate compounds. The Lipinski’s “rule of 5” was a pioneering work dealing with the physicochemical properties of
compounds. Thus, several investigations have reported the physicochemical properties of compounds. The representative descriptors of physicochemical properties are molecular weight, partition coefficient (cLog P, Log D), the number of hydrogen bond donors and acceptors, polar surface area (PSA), the number of the rotatable bonds, and so on. Later, the geometrical properties, that is, descriptors concerning the molecular complexity were taken into account. Indeed, the more complex the molecular structure, that is, the fewer the number of the structurally flat moieties in molecules, the more drug-like the molecule. For example, molecules with more flat aromatic rings tend to have decreased solubility, and have been reported to display increased inhibition of the cytochrome P450 variant CYP 3A4 and the potassium channel hERG. As a result, such compounds have been presumed to be less drug-like compounds. The representative descriptors of geometrical properties are the number of aromatic rings, Fsp (the number of sp hybridized carbons versus the number of total carbons), FM (the size of the molecular framework versus the size of the whole molecule), and so on.

We recently reported the synthesis of 1,3,5-trioxazatriquinane derivatives (Figure 1). One of the 1,3,5-trioxazatriquinane derivatives, SYK-146 (Figure 1) showed selective kappa opioid receptor agonist activity. SYK-146 was identified by a screening of the mini-compound library comprising twelve 1,3,5-trioxazatriquinane derivatives. SYK-146 fulfills several criteria of descriptors of physicochemical as well as geometrical properties: molecular weight, 355.39; cLog P, 2.8727; the numbers of hydrogen bond donors and acceptors, two and six, respectively; topological PSA, 71.39 Å²; the number of rotatable bonds, two; the number of aromatic rings, two; Fsp, 0.4. The outcome suggested that the 1,3,5-trioxazatriquinane skeleton would be druggable and that was expected to provide a promising library of compounds with a high hit rate in the lead discovery process. 1,3,5-Trioxazatriquinane derivatives were prepared from key intermediates 3, which were obtained by reacting an ammonia equivalent like ammonium chloride with α-hydroxyaldehyde 2 derived from the corresponding carbonyl compounds. Oxazoline 3 could be isolated, which enabled us to access not only symmetrical 1,3,5-trioxazatriquinane derivatives 1a (R₁=R₃=R₅=R', R₂=R₄=R₆=R''), but also dissymmetrical ones 1b (R₁=R₃=R', R₂=R₄=R'', R₅=R'''', R₆=R''''') comprised of two identical carbonyl compounds and one more of a different structure (Scheme 1). Although we have selectively synthesized various symmetrical and dissymmetrical derivatives 1a and 1b according to such synthetic methods, 1,3,5-trioxazatriquinane derivatives 1 consisting of three distinct carbonyl compounds (R₁≠R₃≠R₅, R₂≠R₄≠R₆) have never been synthesized selectively. Herein, we report an efficient synthetic method to obtain dissymmetrical 1,3,5-trioxazatriquinane derivatives 1 (R₁≠R₃≠R₅, R₂≠R₄≠R₆).
RESULTS AND DISCUSSION

The optimization of the protecting groups in an α-hydroxyaldehyde

To prepare dissymmetrical 1,3,5-trioxazatriquinane derivatives 1 (R¹ ≠ R³ ≠ R⁵, R² ≠ R⁴ ≠ R⁶), key intermediate oxazolines 3 consisting of two distinct α-hydroxyaldehydes were required. Although such oxazolines 3 could be obtained from two different α-hydroxyaldehydes according to our reported method, oxazolines 3 comprised of identical α-hydroxyaldehydes were also provided concomitantly (see the Supporting Information for details). On the other hand, the reaction of free α-hydroxyaldehydes with α-hydroxyaldehydes having a protected hydroxy group could theoretically two oxazolines 3: one being the objective oxazoline and the other by-products of self-reaction of free α-hydroxyaldehydes. Optimized reaction conditions would suppress the production of the by-product. Therefore, we attempted to investigate protecting groups for an α-hydroxyaldehyde and chose trimethylsilyl (TMS), tert-butylidemethylsilyl (TBS), benzyl (Bn), p-methoxybenzyl (PMB), methoxymethyl (MOM), and 2-methoxyethoxymethyl (MEM) groups as protecting groups of the α-hydroxy group.

The protected α-hydroxyaldehyde 4, which was prepared by the reported method, reacted with α-hydroxyaldehyde 5 to furnish a complex mixture. This complex mixture furnished not only the desired oxazolines 7 and the possible by-product 9, but also the unexpected oxazolines 6 and 8 were observed by MS analysis (Scheme 2). These results suggested that the TMS protecting group was so labile that it was

Scheme 1. Summary of the synthesis of symmetrical 1,3,5-trioxazatriquinane derivatives 1a and dissymmetrical ones 1b
cleaved during the reaction. Therefore, we examined the less labile TBS group. However, protected \( \alpha \)-hydroxyaldehyde 11 with TBS group was not obtained by the similar method used to prepare 4; the attempt toward reduction of the nitrile 10 furnished recovery of the starting material (Scheme 3).

Scheme 2. Reaction with the protected \( \alpha \)-hydroxyaldehyde 4 and free \( \alpha \)-hydroxyaldehyde 5

Scheme 3. Attempt toward preparation of the protected \( \alpha \)-hydroxyaldehyde 11 with TBS group

We next examined the protection by Bn and PMB groups. According to the previously reported method, primary alcohol 13 was prepared from \( \alpha \)-methylstyrene (12). Alcohol 13 was oxidized to give protected \( \alpha \)-hydroxyaldehyde 15 (Scheme 4). The reaction of protected \( \alpha \)-hydroxyaldehyde 15 with free \( \alpha \)-hydroxyaldehyde 5 in \( \text{NH}_3/\text{MeOH} \) provided the objective oxazoline 17 in 69% yield with by-product 9 (Scheme 5). Protected \( \alpha \)-hydroxyaldehyde 16 with the PMB group, which was also synthesized by a similar procedure used to prepare 15, also yielded the objective oxazoline 18 in 37% yield with by-product 9 (Schemes 4 and 5). We attempted to remove the Bn group. Hydrogenolysis with Pd/C under hydrogen furnished a recovery of the starting material. The reaction conditions using 1,4-cyclohexadiene instead of hydrogen yielded a complex mixture. Ultimately, the PMB group in oxazoline 18 was successfully deprotected using DDQ to give oxazoline 8. Oxazoline 8 was treated with glycolaldehyde dimer in the presence of camphorsulfonic acid (CSA) to afford the 1,3,5-trioxazatriquinane derivatives 19a-d in 14% (two-step yield) as a mixture of diastereomers (Scheme 6).

Scheme 4. Synthesis of protected \( \alpha \)-hydroxyaldehydes 15 and 16 with respective Bn and PMB group
Next, we examined MOM and MEM groups as the protecting groups. The hydroxy group in alcohol 20 was protected by MOM and MEM groups, followed by deprotection of the TBS group, oxidation of the resulting primary alcohols to give protected α-hydroxyaldehydes 25 and 26, respectively (Scheme 7). The reaction of protected α-hydroxyaldehydes 25 and 26 with free α-hydroxyaldehyde 5 successfully afforded the objective oxazolines 27 and 28 in 13% and 27% yields, respectively, with by-product 9 (Scheme 8). Deprotection of the MOM group in oxazoline 27 under acidic conditions lead to decomposition. On the other hand, the MEM group in oxazoline 28 was smoothly removed with zinc bromide to give oxazoline 8 in 84% yield (Scheme 9).

The above results suggested that the PMB and the MEM groups were optimal protecting groups for synthesis of oxazoline 8.

Scheme 5. Reaction with protected α-hydroxyaldehyde 15 or 16 and α-hydroxyaldehyde 5

Scheme 6. Deprotection of Bn and PMB groups in respective oxazoline 17 and 18, and synthesis of the 1,3,5-trioxazatriquinane derivatives 19a-d from 18

Scheme 7. Synthesis of protected α-hydroxyaldehydes 25 and 26 with respective MOM and MEM group

Scheme 8. Reaction with protected α-hydroxyaldehyde 25 or 26 and α-hydroxyaldehyde 4
The optimization of the reaction conditions for selective synthesis of oxazoline intermediate with distinct aryl groups

With the optimal protecting groups in hand, we attempted to optimize the reaction conditions in order to selectively obtain the objective oxazoline 18 from the protected α-hydroxyaldehyde 16 with the PMB group because the yield of 18 was higher than that of oxazoline 28 with the MEM group.

To prevent the formation of the by-product 9, which derived from the self-reaction of free α-hydroxaldehyde 5, free α-hydroxaldehyde 5 was slowly added to a MeOH solution of the protected α-hydroxyaldehyde 16, NH₄Cl, and AcONa (Table 1). The slow addition was carried out using a syringe pump. After the completion of the slow addition, the reaction mixture was stirred for one hour under reflux. Although the objective oxazoline 18 was obtained at the flow rate of 2.0 mL/h, by-product 9 as well as a considerable amount of unreacted α-hydroxyaldehyde 5 were determined by ¹H NMR analysis of the crude product (entry 1). The slower the flow rates, the lesser the amounts of both by-product 9 and unreacted free α-hydroxaldehyde 5 were obtained. Eventually, at the flow rate of 0.333 mL/h, the objective oxazoline 18 was selectively obtained in 66% yield with a trace amount of by-product 9 (entry 4, Scheme 10).

With the optimal reaction conditions in hand, we applied the reaction conditions to the reaction of 5 with protected α-hydroxyaldehyde 26 with the MEM group. However, the reaction did not go to completion: free α-hydroxyaldehyde 5, protected α-hydroxyaldehyde 26, objective oxazoline 28, and by-product 9 were observed by ¹H NMR analysis of the crude product.
Table 1. The examination of the flow rates of free α-hydroxyaldehyde $^5$a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow rate (mL/h)</th>
<th>Reaction time (h)</th>
<th>Results ($^1$H NMR analysis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>1</td>
<td>remaining 5 and 16</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>2</td>
<td>remaining 5 (trace) and 16</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>4</td>
<td>remaining 5 (trace) and 16</td>
</tr>
<tr>
<td>4</td>
<td>0.333</td>
<td>6</td>
<td>remaining only 16</td>
</tr>
</tbody>
</table>

$^5$Free α-hydroxyaldehyde 5 (0.074 mmol) in MeOH (2 mL) was slowly added to a MeOH solution (1 mL) of protected α-hydroxyaldehyde 16 (0.089 mmol), NH$_4$Cl (0.148 mmol), and AcONa (0.296 mmol) under reflux with stirring. The slow addition was carried out using a syringe pump at the indicated flow rate. After the completion of the slow addition, the reaction mixture was stirred for 1 h under reflux.

The synthesis of 1,3,5-trioxazatriquinane derivatives 19 and 33

As the oxazolines 18 were selectively obtained as a mixture of diastereomers under the optimal reaction conditions, we attempted to convert 18 into dissymmetrical 1,3,5-trioxazatriquinanes 19a-d. The PMB group in 18 was deprotected using DDQ to give 8, which was treated with glycolaldehyde dimer in the presence of CSA to provide dissymmetric 1,3,5-trioxazatriquinane derivatives 19a-d in yields of 7.7%, 2.6%, 2.5%, and 0.9%,$^{15}$ respectively (Scheme 10). The relative configurations of 19a-d were determined by ROESY and HMBC experiments (see the Supporting Information for details).

Scheme 10. Synthesis of 1,3,5-trioxazatriquinane derivatives 19a-d via oxazoline 18
Using the same procedure, dissymmetric 1,3,5-trioxazatriquinanes 33a-d were synthesized in respective 4.9%, 11.7%, 3.1%, and 1.8% yields from protected \( \alpha \)-hydroxyaldehyde 29 and free \( \alpha \)-hydroxyaldehyde 30 (Scheme 11). 1,3,5-Trioxazatriquinanes 19a-d and 33a-d consisted of all eight possible diastereomers.

Scheme 11. Synthesis of 1,3,5-trioxazatriquinane derivatives 33a-d via oxazoline 31

**CONCLUSION**

We developed a selective synthetic method for dissymmetrical 1,3,5-trioxazatriquinane derivatives 19a-d and 33a-d comprised of three different carbonyl compound equivalents. Our method has three distinguishing features: (1) free \( \alpha \)-hydroxyaldehydes reacted with \( \alpha \)-hydroxyaldehydes bearing protected hydroxy groups; (2) the optimal protecting group of \( \alpha \)-hydroxyaldehydes was the PMB group; and (3) the slow addition of free \( \alpha \)-hydroxyaldehydes to protected \( \alpha \)-hydroxyaldehydes was essential.

**EXPERIMENTAL**

**General Methods**

NMR spectra were recorded on an Agilent VXR-400 (400 MHz) spectrometer and the chemical shifts were reported as \( \delta \) values (ppm) referenced to tetramethylsilane (TMS). IR spectra were recorded on a JASCO FT/IR-460. MS were obtained on JMS-T100LP by an electrospray ionization (ESI) method. Reaction progress was monitored by TLC on Merck Silica Gel 60 F\textsubscript{254}. The column chromatography was carried out using Fuji Silysia CHROMATOREX\textsuperscript{®} PSQ 60B (60 \( \mu \)m), or Fuji Silysia CHROMATOREX\textsuperscript{®} NH-DM2035 (60 \( \mu \)m). The preparative TLC was carried out Merck Silica Gel 60 F\textsubscript{254} PLC plates. The high-flash column chromatography was carried out using YAMAZEN EPCLC-W-Prep 2XY A-Type and
packed columns (40 µm). The reactions were performed under an argon atmosphere unless otherwise noted.

1-(5-(3-Methoxyphenyl)-5-methyl-2,5-dihydroxyoxazol-2-yl)-1-phenylethanol (a mixture of 8 diastereomers) (8)

To a solution of 28 (2.3 mg, 5.0 µmol) in CH₂Cl₂ (0.4 mL) was added ZnBr₂ (2.3 mg, 5.0 µmol) and refluxed for 4 h with stirring. After cooling to ambient temperature, the reaction mixture was poured into a saturated NaHCO₃ aqueous solution and extracted with CHCl₃. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by preparative TLC (AcOEt : Hexane = 1 : 3) to give compound 8 (1.5 mg, 4.8 µmol) as a colorless oil in 84% yield.


2-((4-Methoxybenzyl)oxy)-2-phenylpropan-1-ol (14)

To a solution of α-methylstyrene (12) (0.5 mL, 3.86 mmol) in PMBOH (12 mL) was added mCPBA (77%, 1.60 g, 9.40 mmol) portionwise with stirring at 0 ºC and then stirred at 40 ºC for 96 h. After cooling to ambient temperature, the reaction mixture was poured into an aqueous solution of sodium sulfite and extracted with CHCl₃. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. After removing PMBOH by distillation under reduced pressure, the residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 6) to give compound 14 (589 mg, 2.16 mmol) as a colorless oil in 56% yield.

HR-MS (ESI): [M+Na]⁺ Calcd. for C₁₇H₂₀NaO₃: 295.1310. Found: 295.1306. IR (film): 3451, 3059, 3032, 2979, 2935, 2870, 2836, 1613, 1514, 1249, 1036, 702 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.76 (s, 3H), 2.18-2.23 (m, 1H), 3.53 (dd, J = 8.9, 11.2 Hz, 1H), 3.74 (dd, J = 4.4, 11.2 Hz, 1H), 3.82 (s, 3H), 4.17 (d, J = 10.5 Hz, 1H), 4.32 (d, J = 10.5 Hz, 1H), 6.89-6.92 (m, 2H), 7.27-7.35 (m, 3H), 7.39-7.43 (m, 2H), 7.48-7.50 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 20.0, 55.3, 64.6, 71.7, 79.9, 113.8, 126.6, 127.6, 128.4, 129.1, 130.8, 142.2, 159.1.

2-(Benzyloxy)-2-phenylpropanal (15)

To a solution of 13 in DMSO (2 mL) were added SO₃·Py (655 mg, 4.1 mmol) and NEt₃ (865 µL, 6.2 mmol) and stirred at rt for 3 h. The reaction mixture was poured into a saturated NaHCO₃ aqueous solution and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 30) to give compound 15 (138 mg, 0.57 mmol) as a colorless oil in 69% yield.
HR-MS (ESI): [M+Na]+ Calcd. for C16H16NaO2: 263.1048. Found: 263.1044. IR (film): 3088, 3063, 3032, 2986, 2935, 2869, 2809, 1737, 1448, 1135, 1028, 736, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.79 (s, 3H), 4.49 (s, 2H), 7.29-7.44 (m, 8H), 7.48-7.51 (m, 2H), 9.62 (s, 1H).

2-((4-Methoxybenzyl)oxy)-2-phenylpropanal (16)
Using the procedure for the preparation of 15, 16 (228 mg, 0.84 mmol) was obtained from 14 (272 mg, 1.0 mmol) as a colorless oil in 84% yield.


2-(1-(Benzyloxy)-1-phenylethyl)-5-(3-methoxyphenyl)-5-methyl-2,5-dihydrooxazole (a mixture of 8 diastereomers) (17)
To a solution of 5 (1.5 mg, 8.3 µmol) and 15 (10 mg, 0.042 mmol) in MeOH (0.5 mL) was added 25% NH₄OH (0.5 mL) and stirred at rt for 0.5 h. The reaction mixture was poured into a saturated NaHCO₃ aqueous solution and extracted with CHCl₃. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 10 – 1 : 3) to give compound 17 (2.3 mg, 5.7 µmol) as colorless oil in 69% yield concomitantly with 9 (0.6 mg, 1.7 µmol) in 21%.


2-(1-((4-Methoxybenzyl)oxy)-1-phenylethyl)-5-(3-methoxyphenyl)-5-methyl-2,5-dihydrooxazole (a mixture of 8 diastereomers) (18)
Conventional method
Using the procedure for the preparation of 17, 18 (65 mg, 0.14 mmol) was obtained from 5 (70 mg, 0.39 mmol) and 16 (210 mg, 0.78 mmol) as a colorless oil in 37% yield concomitantly with 9 (81 mg, 0.24 mmol) in 21%.

Slow addition method (optimal conditions)
To a solution of aldehyde 16 (24.1 mg, 0.089 mmol), NH₄Cl (7.9 mg, 0.148 mmol), and AcONa (24.3 mg, 0.296 mmol) in MeOH (1 mL) was slowly added a solution of α-hydroxyaldehyde 5 (13.3 mg, 0.037 mmol) in MeOH (2 mL) with stirring under reflux conditions using syringe pump (flow rate: 0.333 mL/min). After the completion of the slow addition, the reaction mixture was refluxed for 1 h with
stirring. After cooling to ambient temperature, the reaction mixture was poured into a saturated NaHCO₃ aqueous solution and extracted with CHCl₃. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by high-flash column chromatography to give compound 18 (21.0 mg, 0.049 mmol) as a colorless oil in 66% yield. HR-MS (ESI): [M+Na]⁺ Calcd. for C₂₇H₃₀N: 432.2174. Found: 432.2156.

(2S*,2aS*,4S*,4aS*,6aS*)-4-(3-Methoxyphenyl)-2,4-dimethyl-2-phenyl-1,3,5-trioxazatriquinane (19a), (2R*,2aS*,4S*,4aS*,6aS*)-4-((3-methoxyphenyl)-2,4-dimethyl-2-phenyl-1,3,5-trioxazatriquinane (19b), (2S*,2aS*,4R*,4aS*,6aS*)-4-(3-methoxyphenyl)-2,4-dimethyl-2-phenyl-1,3,5-trioxazatriquinane (19c), and (2R*,2aS*,4R*,4aS*,6aS*)-4-(3-methoxyphenyl)-2,4-dimethyl-2-phenyl-1,3,5-trioxazatriquinane (19d)

To a solution of 18 (1.13 g, 2.62 mmol) in CH₂Cl₂ (70 mL) were added DDQ (1.19 g, 5.23 mmol) and distilled water (3.5 mL) and vigorously stirred at rt for 3.5 h. The reaction mixture was poured into a saturated NaHCO₃ aqueous solution and extracted with CH₂Cl₂. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was roughly purified by silica gel column chromatography (AcOEt : Hexane = 1 : 5) to give 8 containing some impurities (317 mg) as colorless oil. To a solution of roughly purified 8 (174 mg) in CHCl₃ (9.0 mL) were added glycolaldehyde dimder (202 mg, 1.68 mmol), and CSA (781 mg, 3.36 mmol) at rt, and stirred for 24 h. The reaction mixture was poured into a saturated NaHCO₃ aqueous solution and extracted with CHCl₃. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 5) and NH-silica gel column chromatography (r-BuOH : Hexane = 1 : 50) repeatedly to give a mixture of 19a and 19d (43.6 mg, 0.123 mmol, 8.6%), 19b (13.2 mg, 0.0373 mmol, 2.6%), 19c (12.9 mg, 0.0365 mmol, 2.5%) as yellow oils.

Mixture of 19a and 19d

The ratio of 19a and 19d was determined by ¹H NMR analysis as 89 : 11.

HR-MS (ESI): [M+H]⁺ Calcd. for C₂₁H₂₂NO₄: 354.1705. Found: 354.1689. IR (neat): 2932, 1583, 1485, 1265, 1145, 1108, 1072, 1024, 978, 763, 704 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.67 (s, 3.33H), 1.68 (s, 2.67H), 3.788 (dd, J = 2.9, 10.0 Hz, 1H), 3.792 (s, 0.33H), 3.83 (s, 2.67H), 4.28 (d, J = 10.0 Hz, 1H), 5.03 (d, J = 2.8 Hz, 0.89H), 5.05 (d, J = 2.8 Hz, 0.11H), 5.105 (s, 0.89H), 5.113 (s, 0.11H), 5.12 (s, 0.11H), 5.16 (s, 0.89H), 6.78 (dd, J = 1.0, 2.4, 8.2 Hz, 1H), 6.78 (dd, J = 1.0, 2.4, 8.2 Hz, 0.11H), 6.82 (dd, J = 1.1, 2.3, 8.16 Hz, 0.89H), 6.91-6.96 (m, 0.22H), 6.98-7.06 (m, 1.78H), 7.20-7.47 (m, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 24.15, 24.16, 55.3, 71.2, 86.7, 87.2, 95.0, 99.5, 101.4, 111.2, 112.3, 117.3, 124.9, 127.4, 128.5, 129.7, 142.4, 144.1, 159.9.
**19b**

HR-MS (ESI): [M+H]^+ Calcd. for C\textsubscript{21}H\textsubscript{24}NO\textsubscript{4}: 354.1705. Found: 354.1705. IR (neat): 2930, 1583, 1486, 1268, 1119, 1038, 979, 763, 590 cm\textsuperscript{-1}. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): δ 1.44 (s, 3H), 1.58 (s, 3H), 3.80 (s, 3H), 3.89 (dd, \(J= 2.9, 9.9\) Hz, 1H), 4.34 (d, \(J= 9.9\) Hz, 1H), 4.91 (s, 1H), 5.14 (s, 1H), 5.29 (d, \(J= 2.9\) Hz, 1H), 6.80 (dd, \(J= 0.7, 2.6, 8.2\) Hz, 1H), 6.86-6.94 (m, 2H), 7.23-7.43 (m, 4H), 7.48-7.52 (m, 2H). \(^1\)C NMR (100 MHz, CDCl\textsubscript{3}): δ 23.2, 23.9, 55.3, 71.3, 86.9, 87.1, 94.8, 99.8, 101.3, 111.2, 112.2, 117.2, 125.9, 127.1, 127.7, 129.6, 140.9, 144.1, 159.8.

**19c**

HR-MS (ESI): [M+H]^+ Calcd. for C\textsubscript{21}H\textsubscript{24}NO\textsubscript{4}: 354.1705. Found: 354.1694. IR (neat): 2931, 1585, 1489, 1447, 1288, 1230, 1144, 1119, 1046, 763, 701 cm\textsuperscript{-1}. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): δ 1.65 (s, 3H), 1.73 (s, 3H), 3.66 (dd, \(J= 2.8, 10.1\) Hz, 1H), 3.83 (s, 3H), 4.13 (d, \(J= 10.1\) Hz, 1H), 4.87 (s, 1H), 5.09 (d, \(J= 2.8\) Hz, 1H), 5.43 (s, 1H), 6.84 (dd, \(J= 0.8, 2.6, 8.2\) Hz, 1H), 7.04 (ddd, \(J= 0.9, 1.5, 7.7\) Hz, 1H), 7.12 (dd, \(J= 1.7, 2.5\) Hz, 1H), 7.28-7.35 (m, 2H), 7.36-7.43 (m, 2H), 7.43-7.53 (m, 2H). \(^1\)C NMR (100 MHz, CDCl\textsubscript{3}): δ 23.4, 24.5, 55.1, 71.6, 86.8, 87.4, 94.8, 99.6, 101.9, 111.8, 112.3, 117.8, 125.0, 127.5, 128.6, 129.0, 142.6, 142.8, 159.3.

**1-(tert-Butyldimethylsilyloxy)-2-(methoxymethoxy)-2-phenylpropane (21)**

To a solution of 20 (610 mg, 2.3 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) were added MOMCl (418 µL, 5.5 mmol) and DIPEA (1.2 mL, 6.9 mmol) and refluxed for 3 h with string. After cooling to ambient temperature, the reaction mixture was poured into a saturated NaHCO\textsubscript{3} aqueous solution and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were washed with brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 30) to give compound 21 (642 mg, 2.1 mmol) as colorless oil in 91% yield.

HR-MS (ESI): [M+Na]^+ Calcd. for C\textsubscript{17}H\textsubscript{30}NaO\textsubscript{3}Si: 333.1862. Found: 333.1868. IR (film): 2954, 2929, 2884, 2857, 1471, 1255, 1115, 1035, 837, 776 cm\textsuperscript{-1}. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): δ -0.12 (s, 3H), -0.05 (s, 3H), 0.83 (s, 9H), 1.67 (s, 3H), 3.40 (s, 3H), 3.63 (d, \(J= 10.0\) Hz, 1H), 3.72 (d, \(J= 10.0\) Hz, 1H), 4.65 (s, 2H), 7.25-7.27 (m, 1H), 7.31-7.35 (m, 2H), 7.41-7.44 (m, 2H).

**1-(tert-Butyldimethylsilyloxy)-2-((2-methoxyethoxy)methoxy)-2-phenylpropane (22)**

To a solution of 20 (1.0 g, 3.8 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) were added MEMCl (1.0 mL, 9.0 mmol) and DIPEA (2.0 mL, 11 mmol) and refluxed for 12 h with string. After cooling to ambient temperature, the reaction mixture was poured into a saturated NaHCO\textsubscript{3} aqueous solution and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were washed with brine, dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure.

HR-MS (ESI): [M+Na]^+ Calcd. for C\textsubscript{17}H\textsubscript{30}NaO\textsubscript{3}Si: 333.1862. Found: 333.1868. IR (film): 2954, 2929, 2884, 2857, 1471, 1255, 1115, 1035, 837, 776 cm\textsuperscript{-1}. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): δ -0.12 (s, 3H), -0.05 (s, 3H), 0.83 (s, 9H), 1.67 (s, 3H), 3.40 (s, 3H), 3.63 (d, \(J= 10.0\) Hz, 1H), 3.72 (d, \(J= 10.0\) Hz, 1H), 4.65 (s, 2H), 7.25-7.27 (m, 1H), 7.31-7.35 (m, 2H), 7.41-7.44 (m, 2H).
reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 30) to give compound 22 (1.2 g, 3.3 mmol) as a colorless oil in 87% yield.

HR-MS (ESI): [M+Na]^+ Calcd. for C_{19}H_{34}NaO_{4}Si: 377.2124. Found: 377.2111. IR (film): 2953, 2928, 2884, 2858, 1254, 1107, 1035, 837 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ -0.13 (s, 3H), -0.06 (s, 3H), 0.82 (s, 9H), 1.67 (s, 3H), 3.37 (s, 3H), 3.50-3.58 (m, 2H), 3.63 (d, J = 10.0 Hz, 1H), 3.63-3.68 (m, 1H), 3.71 (d, J = 10.0 Hz, 1H), 3.83 (ddd, J = 3.6, 5.6, 10.8 Hz, 1H), 4.72 (d, J = 7.2 Hz, 1H), 4.76 (d, J = 7.2 Hz, 1H), 7.22-7.26 (m, 1H), 7.29-7.33 (m, 2H), 7.40-7.43 (m, 2H).

2-(Methoxymethoxy)-2-phenylpropan-1-ol (23)

To a solution of 21 (370 mg, 1.2 mmol) in THF (5.0 mL) was added 1 M solution of TBAF in THF (1.8 mL) at 0 ºC and stirred at rt for 1 h. The reaction mixture was poured into a saturated NaHCO_3 aqueous solution and extracted with CHCl_3. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt : Hexane = 1 : 10) to give compound 23 (240 mg, 1.2 mmol) as a colorless oil in quantitative yield.

HR-MS (ESI): [M+Na]^+ Calcd. for C_{11}H_{16}NaO_{3}: 219.0997. Found: 219.0995. IR (film): 3452, 2983, 2938, 2888, 1446, 1146, 1027, 701 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ 1.59 (s, 3H), 3.03 (dd, J = 6.1, 8.3 Hz, 1H), 3.46 (s, 3H), 3.67 (dd, J = 8.3, 12.2 Hz, 1H), 3.85 (dd, J = 6.1, 12.2 Hz, 1H), 4.64 (d, J = 7.3 Hz, 1H), 4.71 (d, J = 7.3 Hz, 1H), 7.28-7.30 (m, 1H), 7.34-7.38 (m, 2H), 7.41-7.43 (m, 2H).

2-((2-Methoxyethoxy)methoxy)-2-phenylpropan-1-ol (24)

Using the procedure for the preparation of 23, 24 (726 mg, 2.8 mmol) was obtained from 22 (1.0 mg, 2.8 mmol) as a colorless oil in quantitative yield.

HR-MS (ESI): [M+Na]^+ Calcd. for C_{13}H_{20}NaO_{4}: 263.1259. Found: 263.1247. IR (film): 3466, 2980, 2930, 2882, 2819, 1447, 1088, 1055, 1027, 701 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ 1.57 (s, 3H), 3.39 (s, 3H), 3.48 (dd, J = 5.6, 8.8 Hz, 1H), 3.56 (d, J = 4.2 Hz, 1H), 3.57 (d, J = 4.8 Hz, 1H), 3.75 (dd, J = 8.8, 12.4 Hz, 1H), 3.76-3.81 (m, 1H), 3.82-3.88 (m, 1H), 3.92 (dd, J = 5.4, 12.3 Hz, 1H), 4.70 (d, J = 7.8 Hz, 1H), 4.77 (d, J = 7.8 Hz, 1H), 7.25-7.28 (m, 1H), 7.33-7.41 (m, 4H).

2-(Methoxymethoxy)-2-phenylpropanal (25)

Using the procedure for the preparation of 15, 25 (141 mg, 0.73 mmol) was obtained from 23 (228 mg, 1.2 mmol) as a colorless oil in 62% yield.

HR-MS (ESI): [M+Na]^+ Calcd. for C_{11}H_{14}NaO_{3}: 217.0841. Found: 217.0838. IR (film): 3434, 3061, 3027, 2979, 2935, 2895, 1718, 1685, 1447, 1268, 1101, 991, 701 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ 1.70 (s,
2-(2-Methoxyethoxy)methoxy-2-phenylpropanal (26)

Using the procedure for the preparation of 15, 26 (386 mg, 1.6 mmol) was obtained from 24 (500 mg, 2.1 mmol) as a colorless oil in 78% yield.

HR-MS (ESI): [M+Na]+ Calcd. for C_{13}H_{18}NaO_{4}: 261.1103. Found: 261.1091. IR (film): 2985, 2929, 2887, 2817, 1732, 1023 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.71 (s, 3H), 3.37 (s, 3H), 3.51-3.53 (m, 2H), 3.70-3.75 (m, 1H), 3.85-3.90 (m, 1H), 4.88 (d, J = 7.5 Hz, 1H), 4.96 (d, J = 7.5 Hz, 1H), 7.30-7.34 (m, 1H), 7.36-7.44 (m, 4H), 9.51 (s, 1H).

2-(1-(Methoxymethoxy)-1-phenylethyl)-5-(3-methoxyphenyl)-5-methyl-2,5-dihydrooxazole (mixture of 8 diastereomers) (27)

Using the procedure for the preparation of 17, 27 (6.4 mg, 0.018 mmol) was obtained from 25 (132 mg, 0.68 mmol) and 5 (24 mg, 0.14 mmol) as a colorless oil in 13% yield.


2-(1-((2-Methoxyethoxy)methoxy)-1-phenylethyl)-5-(3-methoxyphenyl)-5-methyl-2,5-dihydrooxazole (mixture of 8 diastereomers) (28)

Using the procedure for the preparation of 17, 28 (34 mg, 0.085 mmol) was obtained from 26 (376 mg, 1.6 mmol) and 5 (57 mg, 0.32 mmol) as a colorless oil in 27% yield.

HR-MS (ESI): [M+Na]+ Calcd. for C_{23}H_{29}NNaO_{4}: 422.1943. Found: 422.1935.

2-(1-((4-Methoxybenzyl)oxy)-1-(3-methoxyphenyl)ethyl)-5-methyl-5-phenyl-2,5-dihydrooxazole (mixture of 8 diastereomers) (31)

Using the procedure for the preparation of 18 (optimal condition), 31 (24.3 mg, 0.056 mmol) was obtained from 29 (26.8 mg, 0.089 mmol) and 30 (11.1 mg, 0.074 mmol) as a colorless oil in 76% yield.


(2S*,2aS*,4S*,4aS*,6aS*)-2-(3-Methoxyphenyl)-2,4-dimethyl-4-phenyl-1,3,5-trioxazatriquinane (33a), (2R*,2aS*,4S*,4aS*,6aS*)-2-(3-methoxyphenyl)-2,4-dimethyl-4-phenyl-1,3,5-trioxazatriquinane (33b), (2S*,2aS*,4R*,4aS*,6aS*)-2-(3-methoxyphenyl)-2,4-dimethyl-4-phenyl-1,3,5-trioxazatriquinane (33c), and (2R*,2aS*,4R*,4aS*,6aS*)-2-(3-methoxyphenyl)-2,4-dimethyl-4-phenyl-1,3,5-trioxazatriquinane (33d)
Using the procedure for the preparation of 19a-d, 33a (20.9 mg, 0.059 mmol), 33b (49.8 mg, 0.141 mmol, 11.7%), 33c (13.1 mg, 0.037 mmol, 3.1%), and 33d (7.7 mg, 0.022 mmol, 1.8%) were obtained from 31 (550 mg, 1.27 mmol) as yellow oils.

33a

HR-MS (ESI): [M+H]^+ Calcd. for C_{21}H_{24}NO_4: 354.1705. Found: 354.1693. IR (neat): 2932, 1583, 1486, 1287, 1265, 1144, 1114, 1071, 1024, 978, 704 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ 1.68 (s, 6H), 3.7938 (dd, J = 2.9, 9.9 Hz, 1H), 3.7944 (s, 3H), 4.28 (d, J = 10 Hz, 1H), 5.05 (dd, J = 2.8 Hz, 1H), 5.12 (s, 1H), 5.13 (s, 1H), 6.78 (dd, J = 0.9, 2.4, 8.2 Hz, 1H), 6.90-6.98 (m, 2H), 7.21-7.49 (m, 6H). ^13C NMR (100 MHz, CDCl_3): δ 24.1, 24.2, 55.3, 71.2, 86.7, 87.2, 95.1, 99.5, 101.4, 111.3, 112.1, 117.4, 124.8, 127.4, 128.6, 129.5, 142.3, 144.3, 159.8.

33b

HR-MS (ESI): [M+Na]^+ Calcd. for C_{21}H_{23}NNaO_4: 376.1525. Found: 376.1518. IR (neat): 2930, 1585, 1489, 1288, 1221, 1072, 1042, 885, 763, 701 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ 1.46 (s, 3H), 1.57 (s, 3H), 3.86 (s, 3H), 3.89 (dd, J = 2.9, 9.9 Hz, 1H), 4.34 (d, J = 9.9 Hz, 1H), 4.87 (s, 1H), 5.15 (s, 1H), 5.28 (d, J = 2.8 Hz, 1H), 6.85 (dd, J = 0.8, 2.6, 8.2 Hz, 1H), 7.07 (dd, J = 0.9, 1.5, 7.7 Hz, 1H), 7.12 (dd, J = 1.7, 2.5 Hz, 1H), 7.21-7.38 (m, 6H). ^13C NMR (100 MHz, CDCl_3): δ 23.2, 24.0, 55.2, 71.2, 86.9, 87.0, 94.8, 99.7, 101.3, 112.3, 112.4, 118.3, 124.8, 127.4, 128.5, 128.7, 142.2, 142.5, 159.1.

33c

HR-MS (ESI): [M+H]^+ Calcd. for C_{21}H_{24}NO_4: 354.1705. Found: 354.1700. IR (neat): 2932, 1583, 1486, 1287, 1265, 1144, 1114, 1071, 1024, 978, 704 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ 1.67 (s, 3H), 1.73 (s, 3H), 3.66 (dd, J = 2.8, 10.1 Hz, 1H), 3.84 (s, 3H), 4.11 (d, J = 10.1 Hz, 1H), 4.88 (s, 1H), 5.11 (d, J = 2.8 Hz, 1H), 5.43 (s, 1H), 6.85 (dd, J = 1.0, 2.3, 8.2 Hz, 1H), 7.01-7.08 (m, 2H), 7.27-7.56 (m, 6H). ^13C NMR (100 MHz, CDCl_3): δ 23.3, 24.4, 55.3, 71.5, 86.8, 87.4, 94.9, 99.6, 101.9, 111.1, 112.5, 117.4, 125.5, 127.3, 128.0, 129.7, 141.1, 144.4, 159.9.

33d

HR-MS (ESI): [M+Na]^+ Calcd. for C_{21}H_{23}NNaO_4: 376.1525. Found: 376.1513. IR (neat): 2927, 1603, 1489, 1454, 1381, 1276, 1223, 1170, 1119, 1041, 763, 698 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ 1.55 (s, 3H), 1.70 (s, 3H), 3.76 (dd, J = 2.7, 10.1 Hz, 1H), 3.83 (s, 3H), 4.19 (d, J = 10.1 Hz, 1H), 4.92 (s, 1H), 5.14 (s, 1H), 5.33 (d, J = 2.8 Hz, 1H), 6.88 (dd, J = 0.8, 2.6, 8.2 Hz, 1H), 7.06-7.43 (m, 8H). ^13C NMR (100 MHz, CDCl_3): δ 22.6, 23.1, 55.2, 71.6, 86.96, 87.03, 94.6, 100, 101.9, 111.9, 112.9, 118.3, 125.4, 127.1, 127.8, 128.7, 141.0, 142.3, 159.2.

REFERENCES AND NOTES


7. These values were calculated using ChemDraw Professional version 16.0.


9. Synthetic methods of symmetrical and dissymmetrical 1,3,5-trioxazatriquinane derivatives 1 were described for details in the Supporting Information.


15. The reaction proceeded smoothly to give the objective compounds with a small amount of by-products. However, repeated purifications were required because the Rf values of the objective products and by-products were so close. Therefore, repeated purifications lead poor isolated yields.