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

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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.[1] Thus, several investigations have reported the physicochemical properties of compounds.[2,3] 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.[3,4] 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.[4a] 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^3 (the number of sp^3 hybridized carbons versus the number of total carbons), f_{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 **1** (Figure 1).[5] One of the 1,3,5-trioxazatriquinane derivatives, SYK-146 (Figure 1) showed selective kappa opioid receptor agonist activity.[6] 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;[7] the numbers of hydrogen bond donors and acceptors, two and six, respectively; topological PSA, 71.39 Å^2;[7] the number of rotatable bonds, two; the number of aromatic rings, two; Fsp^3, 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 **1** 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** (R^1=R^3=R^5=R', R^2=R^4=R^6=R''), but also dissymmetrical ones **1b** (R^1=R^3=R', R^2=R^4=R'', R^5=R''', R^6=R'''') comprised of two identical carbonyl compounds and one more of a different structure (Scheme 1).[5] Although we have selectively synthesized various symmetrical and dissymmetrical derivatives **1a** and **1b** according to such synthetic methods,[5,6,8] 1,3,5-trioxazatriquinane derivatives **1** consisting of three distinct carbonyl compounds ($R^1 \neq R^3 \neq R^5$, $R^2 \neq R^4 \neq R^6$) have never been synthesized selectively.[9] Herein, we report an efficient synthetic method to obtain dissymmetrical 1,3,5-trioxazatriquinane derivatives **1** ($R^1 \neq R^3 \neq R^5$, $R^2 \neq R^4 \neq R^6$).

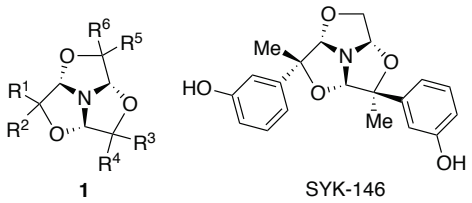
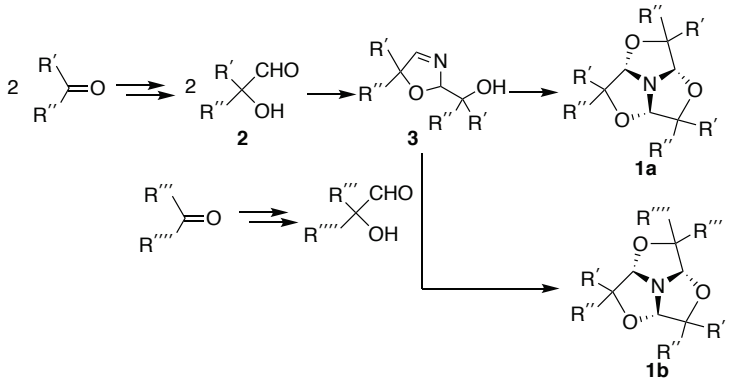


Figure 1. Structures of 1,3,5-trioxazatriquinane derivatives **1** and SYK-146 (selective kappa opioid receptor agonist)



Scheme 1. Summary of the synthesis of symmetrical 1,3,5-trioxazatriquinane derivatives **1a** and dissymmetrical ones **1b**

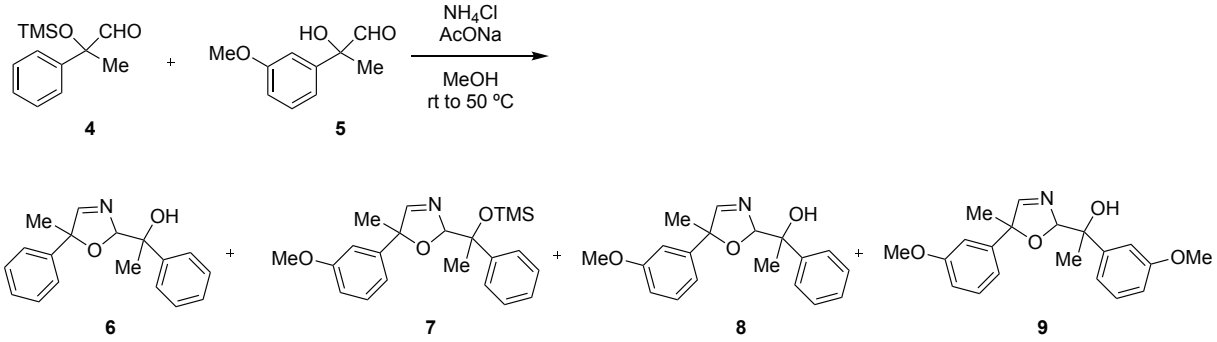
RESULTS AND DISCUSSION

The optimization of the protecting groups in an α-hydroxyaldehyde

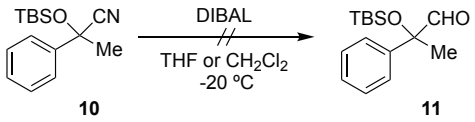
To prepare dissymmetrical 1,3,5-trioxazatriquinane derivatives **1** ($R^1 \neq R^3 \neq R^5$, $R^2 \neq R^4 \neq R^6$), key intermediate oxazolines **3** consisting of two distinct α-hydroxyaldehydes were required. Although such oxazolines **3** could be obtained from two different α-hydroxyaldehydes 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*-butyldimethylsilyl (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,[10a,b] reacted with α-hydroxyaldehyde **5**[6] 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

cleaved during the reaction. Therefore, we examined the less labile TBS group. However, protected α-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).

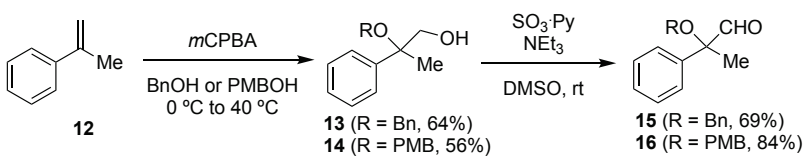


Scheme 2. Reaction with the protected α-hydroxyaldehyde **4** and free α-hydroxyaldehyde **5**

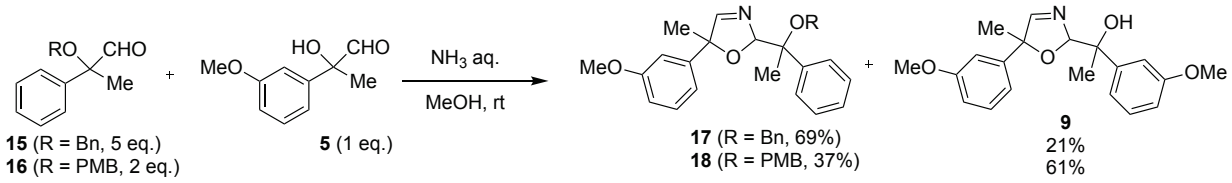


Scheme 3. Attempt toward preparation of the protected α-hydroxyaldehyde **11** with TBS group

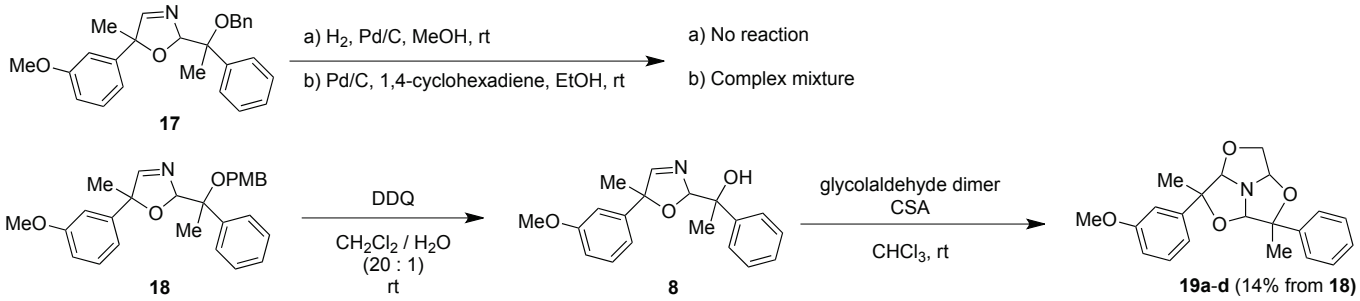
We next examined the protection by Bn and PMB groups. According to the previously reported method, primary alcohol **13** was prepared from α-methylstyrene (**12**).[12] Alcohol **13** was oxidized to give protected α-hydroxyaldehyde **15** (Scheme 4). The reaction of protected α-hydroxyaldehyde **15** with free α-hydroxyaldehyde **5** in NH_3/MeOH provided the objective oxazoline **17** in 69% yield with by-product **9** (Scheme 5). Protected α-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[13] 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 α-hydroxyaldehydes **15** and **16** with respective Bn and PMB group



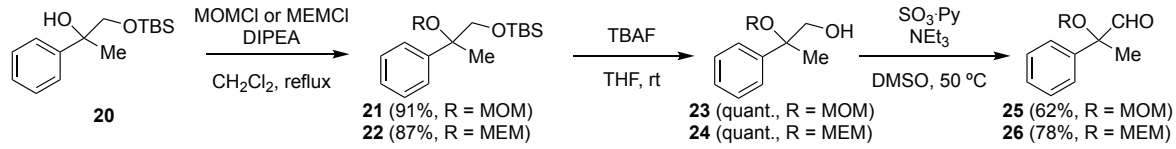
Scheme 5. Reaction with protected α-hydroxyaldehyde **15** or **16** and α-hydroxyaldehyde **5**



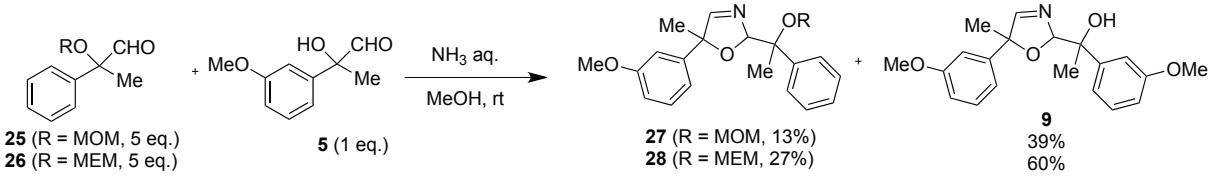
Scheme 6. Deprotection of Bn and PMB groups in respective oxazoline **17** and **18**, and synthesis of the 1,3,5-trioxazatriquinane derivatives **19a**-**d** from **18**

Next, we examined MOM and MEM groups as the protecting groups. The hydroxy group in alcohol **20**[14] 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).

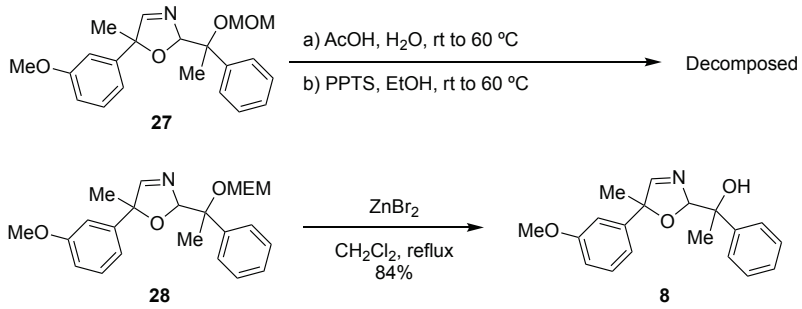
The above results suggested that the PMB and the MEM groups were optimal protecting groups for synthesis of oxazoline **8**.



Scheme 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**



Scheme 9. Deprotection of MOM and MEM groups in respective oxazoline **27** and **28**

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-hydroxyaldehyde **5**, free α-hydroxyaldehyde **5** was slowly added to a MeOH solution of the protected α-hydroxyaldehyde **16**, NH_4Cl, 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 ^{1}H 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-hydroxyaldehyde **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 ^{1}H NMR analysis of the crude product.

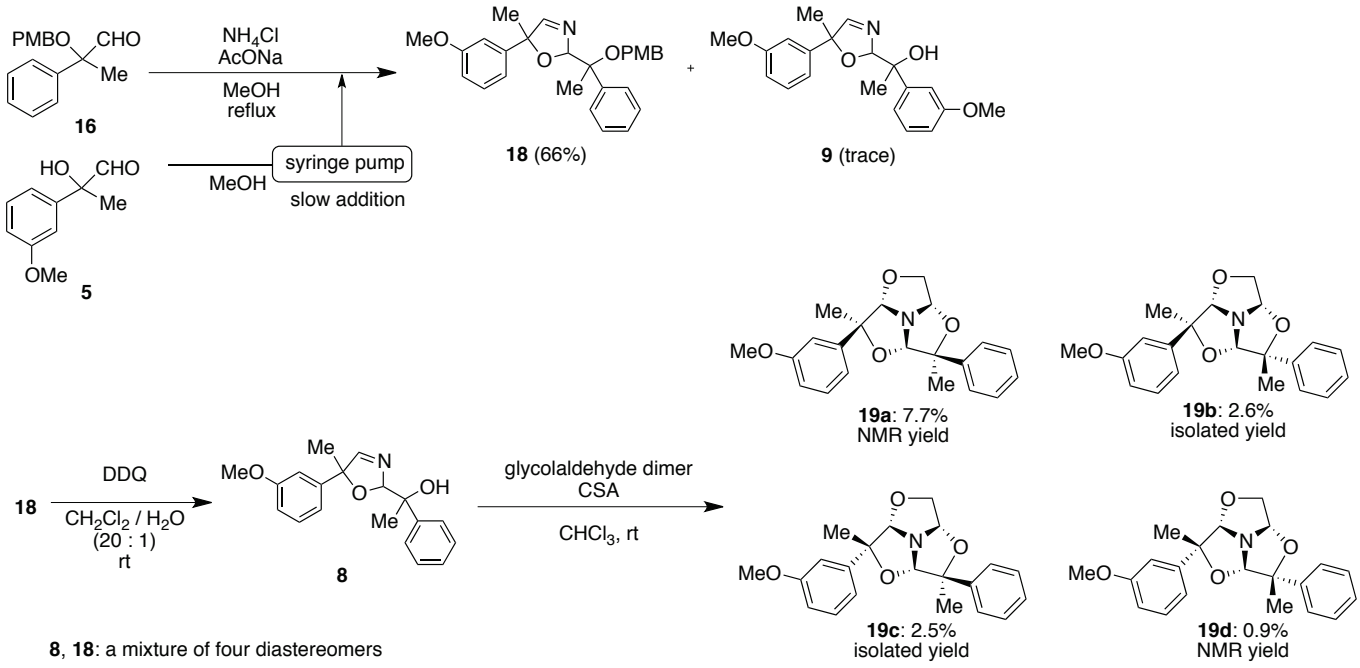
Table 1. The examination of the flow rates of free α-hydroxyaldehyde **5**[a]

Entry	Flow rate (mL/h)	Reaction time (h)	Results (^{1}H NMR analysis)
1	2.0	1	remaining **5** and **16**
2	1.0	2	remaining **5** (trace) and **16**
3	0.5	4	remaining **5** (trace) and **16**
4	0.333	6	remaining only **16**

[a]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_4Cl (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.

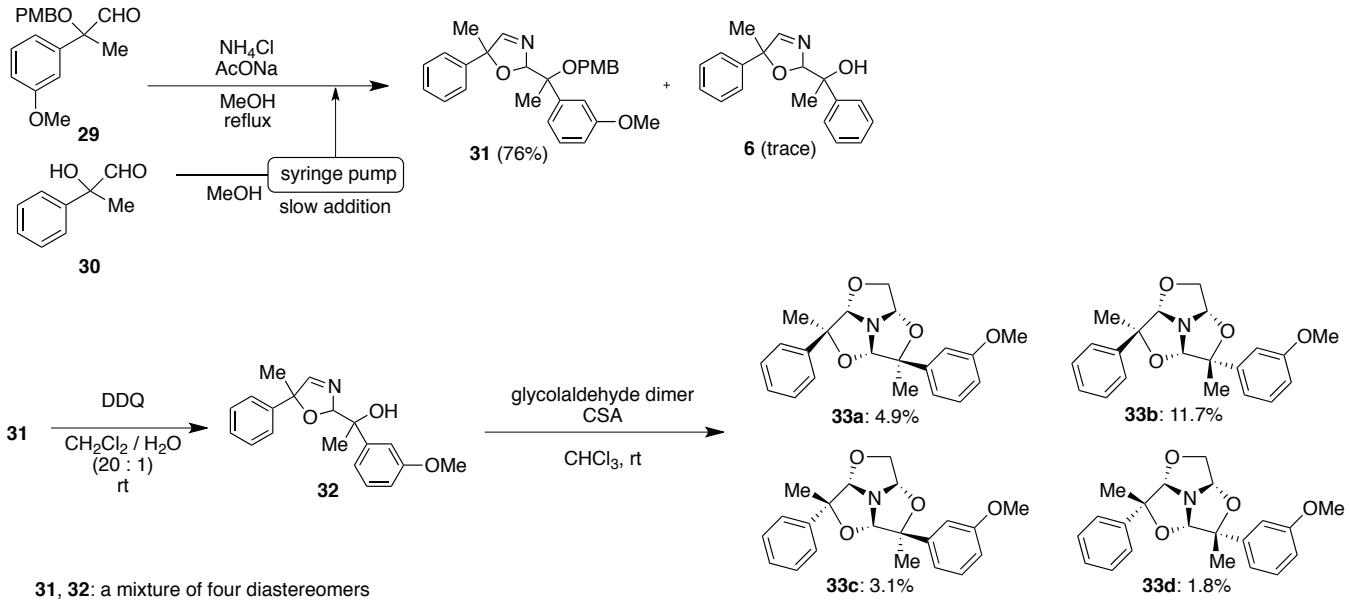
The synthesis of 1,3,5-trioxazatriquinane derivatives 19 and 33

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[15] from protected α-hydroxyaldehyde **29** and free α-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 α-hydroxyaldehydes reacted with α-hydroxyaldehydes bearing protected hydroxy groups; (2) the optimal protecting group of α-hydroxyaldehydes was the PMB group; and (3) the slow addition of free α-hydroxyaldehydes to protected α-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 δ 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_{254}. The column chromatography was carried out using Fuji Silysia CHROMATOREX® PSQ 60B (60 μm), or Fuji Silysia CHROMATOREX® NH-DM2035 (60 μm). The preparative TLC was carried out Merck Silica Gel 60 F_{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 CH_2Cl_2 (0.4 mL) was added $ZnBr_2$ (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 $NaHCO_3$ 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 preparative TLC (AcOEt : Hexane = 1 : 3) to give compound **8** (1.5 mg, 4.8 μmol) as a colorless oil in 84% yield.

HR-MS (ESI): $[M+Na]^+$ Calcd. for $C_{19}H_{21}NNaO_3$: 334.1419. Found: 334.1428.

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 *m*CPBA (77%, 1.60 g, 9.40 mmol) portionewise 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 $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 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 $C_{17}H_{20}NaO_3$: 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, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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**[12] in DMSO (2 mL) were added SO_3·Py (655 mg, 4.1 mmol) and NEt_3 (865 μL, 6.2 mmol) and stirred at rt for 3 h. The reaction mixture was poured into a saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. 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 : 30) to give compound **15** (138 mg, 0.57 mmol) as a colorless oil in 69% yield.

HR-MS (ESI): $[M+Na]^+$ Calcd. for $C_{16}H_{16}NaO_2$: 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, $CDCl_3$): 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.

HR-MS (ESI): $[M+Na]^+$ Calcd. for $C_{17}H_{18}NaO_3$: 293.1154. Found: 293.1145. IR (film): 3060, 3033, 2993, 2936, 2909, 2870, 2836, 2809, 1736, 1613, 1534, 1250, 1334, 1032, 822, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.78 (s, 3H), 3.82 (s, 3H), 4.42 (s, 2H), 6.90-6.93 (m, 2H), 7.31-7.37 (m, 3H), 7.40-7.44 (m, 2H), 7.48-7.51 (m, 2H), 9.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 55.3, 65.4, 84.2, 113.9, 126.7, 128.3, 128.8, 129.1, 130.1, 138.0, 159.3, 199.9.

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% NH_4OH (0.5 mL) and stirred at rt for 0.5 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 – 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%.

HR-MS (ESI): $[M+Na]^+$ Calcd. for $C_{26}H_{27}NNaO_3$: 424.1889. Found: 424.1892.

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), NH_4Cl (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

stirrinig. After cooling to ambient temperature, 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 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 $C_{27}H_{30}N$: 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 CH_2Cl_2 (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 $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 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 $CHCl_3$ (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 $NaHCO_3$ 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 : 5) and NH-silica gel column chromatography (*t*-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 $C_{21}H_{24}NO_4$: 354.1705. Found: 354.1689. IR (neat): 2932, 1583, 1485, 1265, 1145, 1108, 1072, 1024, 978, 763, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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 (ddd, J = 1.0, 2.4, 8.2 Hz, 1H), 6.78 (ddd, J = 1.0, 2.4, 8.2 Hz, 0.11H), 6.82 (ddd, 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{21}H_{24}NO_4$: 354.1705. Found: 354.1705. IR (neat): 2930, 1583, 1486, 1268, 1119, 1038, 979, 763, 590 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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 (ddd, *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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{21}H_{24}NO_4$: 354.1705. Found: 354.1694. IR (neat): 2931, 1585, 1489, 1447, 1288, 1230, 1144, 1119, 1046, 763, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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 (ddd, *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). ^{13}C NMR (100 MHz, $CDCl_3$): 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_2Cl_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 $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. 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 : 30) to give compound **21** (642 mg, 2.1 mmol) as colorless oil in 91% yield.

HR-MS (ESI): $[M+Na]^+$ Calcd. for $C_{17}H_{30}NaO_3Si$: 333.1862. Found: 333.1868. IR (film): 2954, 2929, 2884, 2857, 1471, 1255, 1115, 1035, 837, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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_2Cl_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 $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. 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 : 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 $C_{19}H_{34}NaO_4Si$: 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, 702 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,

3H), 3.45 (s, 3H), 4.76 (d, *J* = 7.2 Hz, 1H), 4.90 (d, *J* = 7.2 Hz, 1H), 7.31-7.35 (m, 1H), 7.38-7.45 (m, 4H), 9.50 (s, 1H).

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, $CDCl_3$): 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.

HR-MS (ESI): $[M+Na]^+$ Calcd. for $C_{21}H_{25}NNaO_4$: 378.1681. Found: 378.1694.

2-(1-((2-Methoxyethoxy)methoxy)-1-phenylethyl)-5-(3-mthoxyphenyl)-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 $C_{23}H_{29}NNaO_5$: 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.

HR-MS (ESI): $[M+Na]^+$ Calcd. for $C_{27}H_{29}NNaO_4$: 454.1994. Found: 454.1972.

(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-trioxzatriquinane (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 (ddd, *J* = 0.9, 2.4, 8.2 Hz, 1H), 6.90-6.98 (m, 2H), 7.21-7.49 (m, 6H). ^{13}C 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 (ddd, *J* = 0.8, 2.6, 8.2 Hz, 1H), 7.07 (ddd, *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). ^{13}C 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): 2930, 1605, 1487, 1448, 1260, 1119, 1069, 1029, 764 , 701 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 (ddd, *J* = 1.0, 2.3, 8.2 Hz, 1H), 7.01-7.08 (m, 2H), 7.27-7.56 (m, 6H). ^{13}C 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 (ddd, *J* = 0.8, 2.6, 8.2 Hz, 1H), 7.06-7.43 (m, 8H). ^{13}C 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

1. C. A. Lipinski, F. Lombardo, B. W. Dominy, and P. J. Feeney, *Adv. Drug Deliv. Rev.*, 1997, **23**, 3.

2. (a) D. F. Veber, S. R. Johnson, H.–Y. Cheng, B. R. Smith, K. W. Ward, and K. D. Kopple, *J. Med. Chem.*, 2002, **45**, 2615; (b) Y. C. Martin, *J. Med. Chem.*, 2005, **48**, 3164; (c) S. A. Hitchcock and L. D. Pennington, *J. Med. Chem.*, 2006, **49**, 7559; (d) M. P. Gleeson, *J. Med. Chem.*, 2008, **51**, 817; (e) J. D. Hughes, J. Blagg, D. A. Price, S. Bailey, G. A. DeCrescenzo, R. V. Devraj, E. Ellsworth, Y. M. Fobian, M. E. Gibbs, R. W. Gilles, N. Greene, E. Huang, T. Krieger-Burke, J. Loesel, T. Wager, L. Whiteley, and Y. Zhang, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 4872; (f) M. J. Waring, *Expert Opin. Drug Discov.*, 2010, **5**, 235.
3. (a) P. D. Leeson, S. A. St-Gallay, and M. C. Wenlock, *Med. Chem. Commun.*, 2011, **2**, 91; (b) S. Nakashima, K. Yamamoto, Y. Arai, and Y. Ikeda, *Chem. Pharm. Bull.*, 2013, **61**, 1228; (c) P. D. Leeson, *Chem. Res. Toxicol.*, 2018, **31**, 494; (d) W. P. Walters, *Expert Opin. Drug Discov.*, 2012, **7**, 99.
4. (a) T. J. Ritchie and S. J. F. Macdonald, *Drug Discov. Today*, 2009, **14**, 1011; (b) F. Lovering, J. Bikker, and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752; (c) T. J. Ritchie, S. J. F. Macdonald, R. J. Young, and S. D. Pickett, *Drug Discov. Today*, 2011, **16**, 164; (d) T. R. Pardhi, M. S. Patel, V. Sudarsanam, and K. K. Vasu, *Med. Chem. Commun.*, 2018, **9**, 1472; (e) T. Luker, L. Alcaraz, K. K. Chohan, N. Blomberg, D. S. Brown, R. J. Butlin, T. Elebring, A. M. Griffin, S. Guile, S. St-Gallay, B.-M. Swahn, S. Swallow, M. J. Waring, M. C. Wenlock, and P. D. Leeson, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 5673; (f) F. Lovering, *Med. Chem. Commun.*, 2013, **4**, 515; (g) M. Aldeghi, S. Malhotra, D. L. Selwood, and A. W. E. Chan, *Chem. Biol. Drug Des.*, 2014, **83**, 450; (h) E. Rincón-Villamizar and G. Restrepo, *Toxicol. Environ. Chem.*, 2014, **96**, 594; (i) O. Méndez-Lucio and J. L. Medina-Franco, *Drug Discov. Today*, 2017, **22**, 120.
5. H. Nagase, A. Watanabe, M. Harada, M. Nakajima, K. Hasebe, H. Mochizuki, K. Yoza, and H. Fujii, *Org. Lett.*, 2009, **11**, 539.
6. S. Hirayama, N. Wada, T. Nemoto, T. Iwai, H. Fujii, and H. Nagase, *ACS Med. Chem. Lett.*, 2014, **5**, 868.
7. These values were calculated using ChemDraw Professional version 16.0.
8. (a) H. Nagase, A. Watanabe, T. Nemoto, M. Nakajima, K. Hasebe, H. Mochizuki, and H. Fujii, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 4023; (b) H. Nagase, K. Koyano, N. Wada, S. Hirayama, A. Watanabe, T. Nemoto, M. Nakajima, K. Nakao, H. Mochizuki, and H. Fujii, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6198; (c) N. Wada, H. Fujii, K. Koyano, S. Hirayama, T. Iwai, T. Nemoto, and H. Nagase, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 7551; (d) S. Hirayama, N. Wada, N. Kuroda, T. Iwai, N. Yamaotsu, S. Hirono, H. Fujii, and H. Nagase, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4895.
9. Synthetic methods of symmetrical and dissymmetrical 1,3,5-trioxazatriquinane derivatives **1** were described for details in the Supporting Information.

10. (a) N. Kurono, M. Yamaguchi, K. Suzuki, and T. Ohkuma, *J. Org. Chem.*, 2005, **70**, 6530; (b) W. A. Vinson, K. S. Prickett, B. Spahic, and P. R. Ortiz de Montellano, *J. Org. Chem.*, 1983, **48**, 4661.
11. M. Golinseki, C. P. Brock, and D. S. Watt, *J. Org. Chem.*, 1993, **58**, 159.
12. K. A. Monk, N. Duncan, E. A. Bauch, and C. M. Garner, *Tetrahedron*, 2008, **64**, 8605.
13. D. E. Thurston, V. S. Murty, D. R. Langley, and G. B. Jones, *Synthesis*, 1990, 81.
14. B. Hatano, S. Toyota, and F. Toda, *Green Chem.*, 2001, **3**, 140.
15. The reaction proceeded smoothly to give the objective compounds with a small amount of by-products. However, repeated purifications were required because the R_f values of the objective products and by-products were so close. Therefore, repeated purifications lead poor isolated yields.