Supporting Information

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

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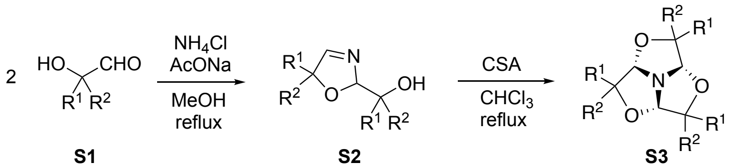
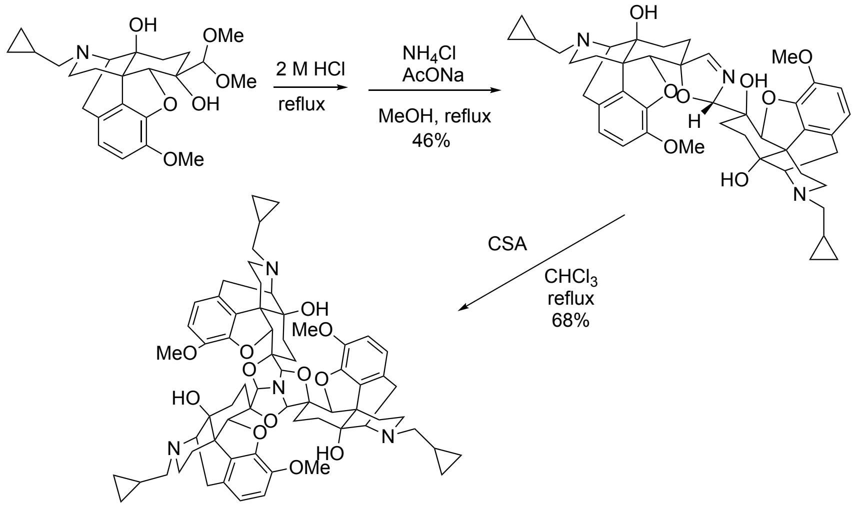
TABLE OF CONTENTS

Synthetic methods of 1,3,5-trioxazatriquinane derivatives

We have already reported the synthesis of symmetrical 1,3,5-trioxazatriquinane derivatives.[1-6] A general synthetic scheme is shown in Scheme S1. α-Hydroxyaldehyde **S1** prepared from the corresponding ketone[1,2] was converted into oxazoline **S2**. A solution of **S2** in $CHCl_3$ was refluxed in the presence of CSA to provide symmetrical 1,3,5-trioxazatriquinane **S3**.[1] The results suggested that a part of oxazoline **S2** was hydrolyzed to give α-hydroxyaldehyde **S1** during the reaction and that **S2** reacted with **S1** prepared *in situ* to provide **S3**. A trace amount of water in the reaction system may catalyze the reaction. The specific example[1] is indicated in Scheme S2.

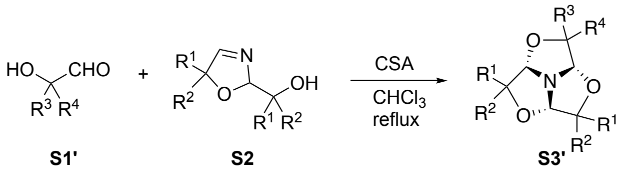


Scheme S1. General synthetic method of symmetrical 1,3,5-trioxazatriquinane **S3**

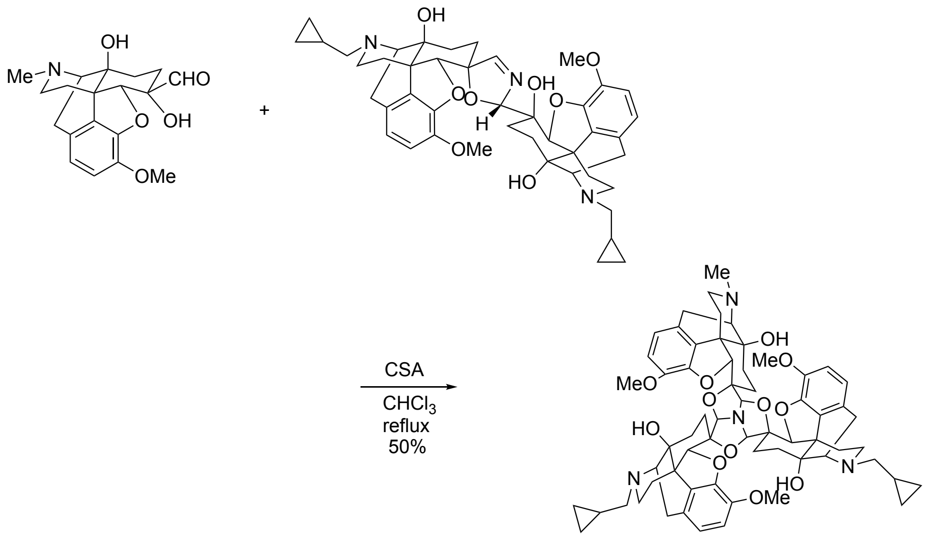


Scheme S2. Specific example of synthesis of symmetrical 1,3,5-trioxazatriquinane[1]

The intermediate oxazoline **S2** could be isolated, which enabled the reaction of **S2** and a second α-hydroxyaldehyde **S1'**. Therefore, dissymmetrical 1,3,5-trioxazatriquinanes **S3'** was selectively obtained (Scheme S3).[1-3] The results suggested that the reaction rate of **S1'** with **S2** would be faster than that of hydrolysis of **S2** in the presence of a catalytic amount of water. The specific example[3] was delineated in Scheme S4.

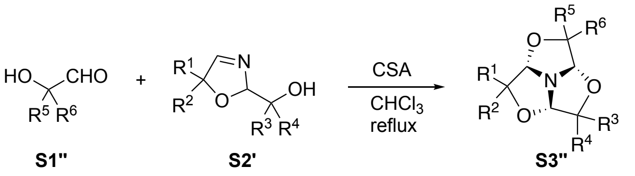


Scheme S3. General synthetic method of dissymmetrical 1,3,5-trioxazatriquinane **S3'**



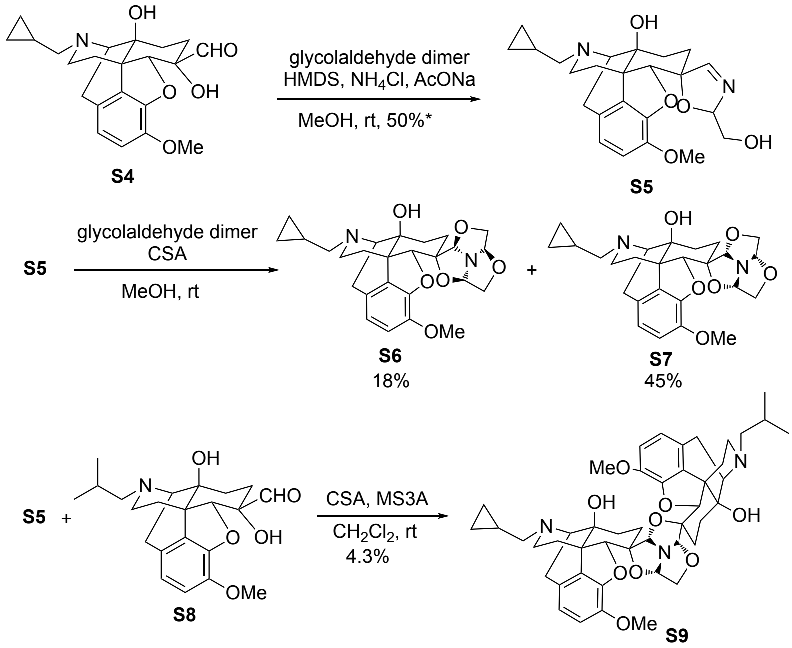
Scheme S4. Specific example of synthesis of dissymmetrical 1,3,5-trioxazatriquinane[3]

Taking into account the results mentioned above, in order to selectively synthesize dissymmetrical 1,3,5-trioxazatriquinanes **S3''** ($R^1 \neq R^3 \neq R^5$, $R^2 \neq R^4 \neq R^6$) it was key to obtain oxazolines **S2'** consisting of two distinct α-hydroxyaldehydes (Scheme S5).



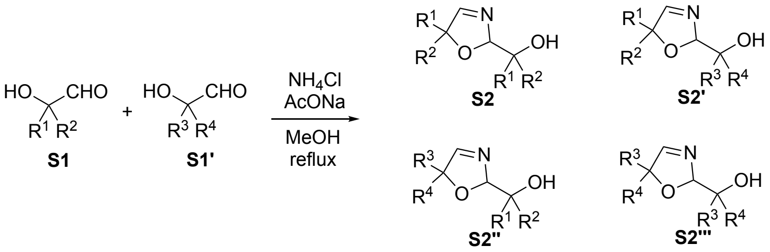
Scheme S5. General synthetic method of dissymmetrical 1,3,5-trioxazatriquinane **S3''**

We have already reported oxazoline **S5** synthesized from **S4** and glycolaldehyde dimer (Scheme S6).[4] Although we examined the reaction of **S4** with various α-hydroxyaldehydes, only the glycolaldehyde selectively gave the objective oxazoline. Oxazoline **S5** reacted with glycolaldehyde dimer to afford 1,3,5-trioxazatriquinanes **S6** and **S7**. However, the obtained 1,3,5-trioxazatriquinanes **S6** and **S7** were comprised of two glycolaldehydes (Scheme S6).[4] We attempted to treat **S5** with α-hydroxyaldehyde **S8** to provide 1,3,5-trioxazatriquinane **S9**, which consisted of three distinct α-hydroxyaldehydes. Unfortunately, the yield was only 4.3% (unpublished results). The results suggested that oxazoline **S5** was easily hydrolyzed.



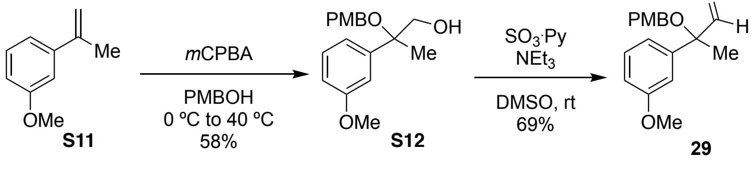
Scheme S6. Synthesis of oxazoline **S5** and dissymmetrical 1,3,5-trioxazatriquinanes **S6**, **S7**, and **S9**.
*The yields were calculated from the corresponding precursor ketone of **S4**

In theory, the reaction of two different α-hydroxyaldehydes **S1** and **S1'** could give the objective oxazoline **S2'**. However, oxazolines **S2**, **S2''**, and **S2'''** were also obtained concomitantly (Scheme S7). Moreover, each oxazoline has eight diastereomers. Therefore, this synthetic tactic was not practical.

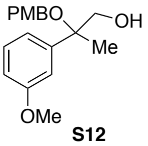


Scheme S7. The reaction of two different α-hydroxyaldehydes **S1** and **S1'**

Synthesis of protected α-hydroxyalehyde 29 with PMB group



2-((4-Methoxybenzyl)oxy)-2-(3-methoxyphenyl)propan-1-ol (S12)

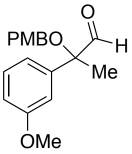


S12

Using the procedure for the preparation of **14**, **S12** (2.35 g, 15.9 mmol) was obtained from **S11**[7] (2.35 g, 15.9 mmol) as a colorless oil in 58% yield.

HR-MS (ESI): $[M+Na]^+$ Calcd. For $C_{18}H_{22}NaO_4$: 325.1416. Found: 325.1419. IR (neat): 2937, 1611, 1514, 1487, 1290, 1249, 1173, 1037, 821, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.73 (s, 3H), 3.53 (d, *J* = 11.2 Hz, 1H), 3.73 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 6H), 4.18 (d, *J* = 10.6 Hz, 1H), 4.32 (d, *J* = 10.6 Hz, 1H), 6.84-6.94 (m, 3H), 7.02-7.08 (m, 2H), 7.25-7.37 (m, 3H), a proton (OH) was not observed. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0, 55.1, 55.2, 64.6, 71.6, 80.0, 112.6, 112.7, 113.8, 118.9, 129.1, 129.4, 130.8, 144.1, 159.1, 159.7.

2-((4-Methoxybenzyl)oxy)-2-(3-methoxyphenyl)propanal (29)

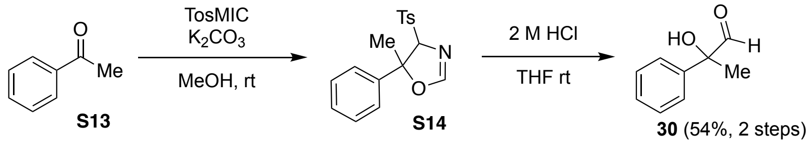


29

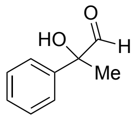
Using the procedure for the preparation of **16**, **29** (104 mg, 0.347 mmol) was obtained from **S12** (194 mg, 0.642 mmol) as a colorless oil in 69% yield.

HR-MS (ESI): $[M+Na]^+$ Calcd. for $C_{18}H_{20}NaO_4$: 323.1259. Found: 323.1249. IR (neat): 2937, 2835, 1733, 1611, 1514, 1252, 1173, 1131, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 4.42 (s, 2H), 6.86-6.93 (m, 3H), 7.02-7.06 (m, 2H), 7.29-7.36 (m, 3H), 9.58 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 55.26, 55.29, 65.5, 84.1, 112.6, 113.7, 113.9, 119.1, 129.1, 129.9, 130.2, 139.7, 159.3, 160.1, 199.5.

Synthesis of free α-hydroxyaldehyde **30**



2-Hydroxy-2-phenylpropanal (30)



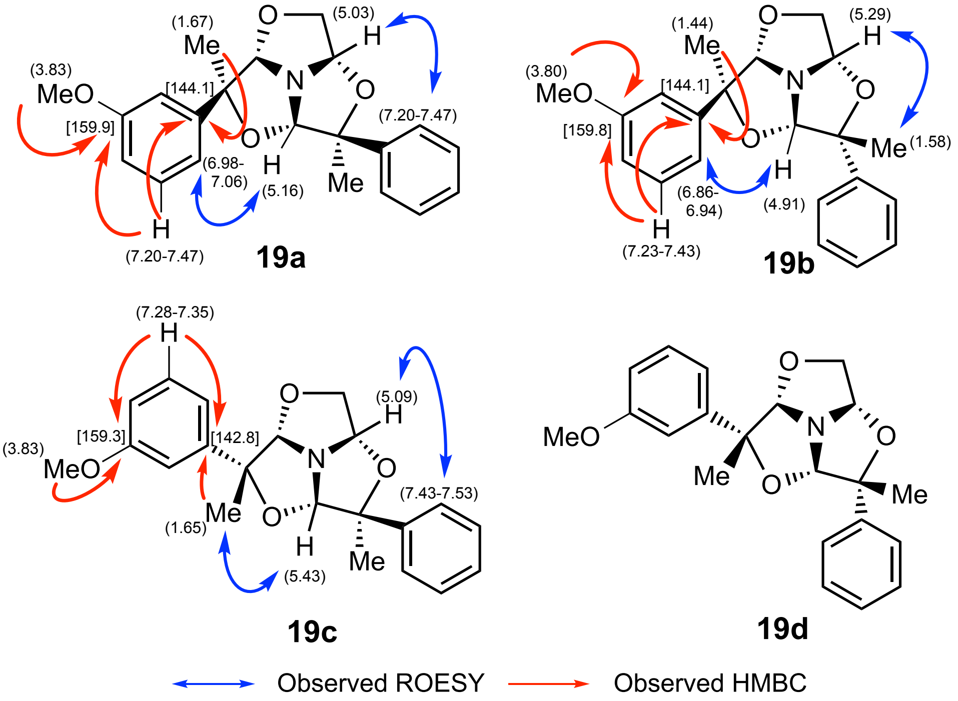
30

Using the reported procedure[5], **30** (2.23 g, 14.9 mmol) was obtained from **S13** (3.00 g, 25.0 mmol) as a colorless oil in 54% yield.

All the physical data were identical to the reported data.[8]

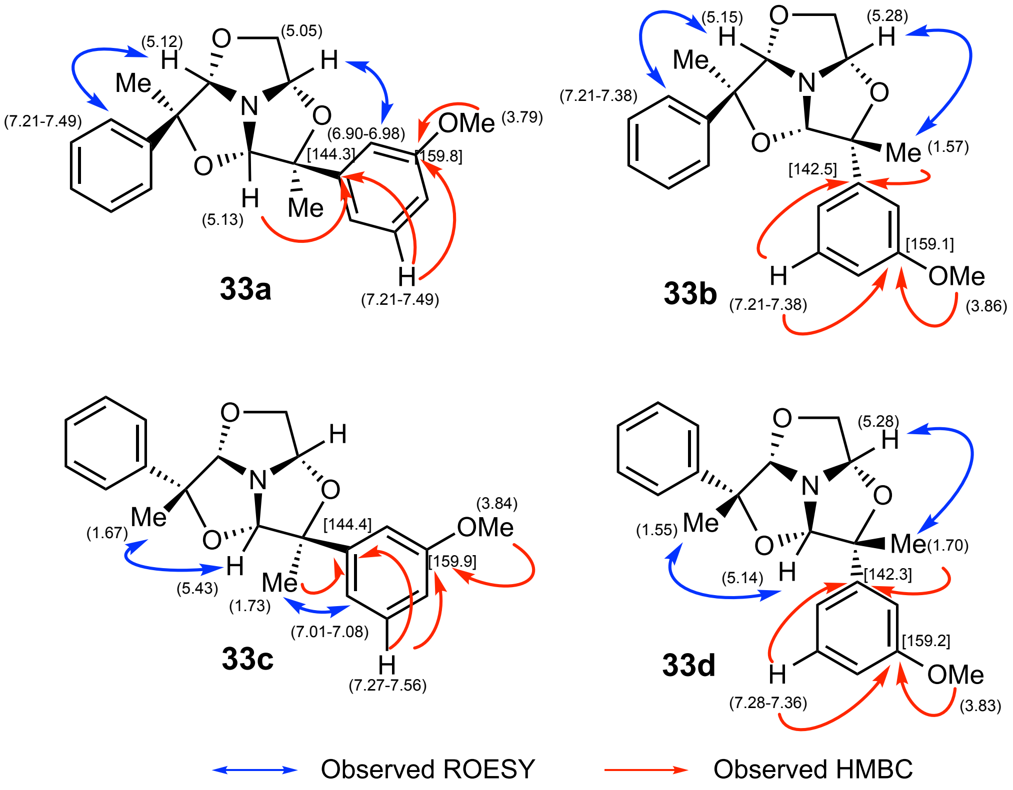
Determination of the relative configurations of 1,3,5-trioxazatriquinanes 19 and 33

The relative configurations of **19a-c** were determined by ROSEY and HMBC experiments.



Values in parentheses and brackets mean chemical shifts of ^{1}H NMR or ^{13}C NMR, respectively.

The relative configurations of **33a-d** were determined by ROSEY and HMBC experiments.



Values in parentheses and brackets mean chemical shifts of ^{1}H NMR or ^{13}C NMR, respectively.

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