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SYNTHESIS OF NOVEL 1,3-DIOXA-5-THIAZATRIQUINANE AND 1-OXA-3,5-DITHIAZATRIQUINANE DERIVATIVES AND THEIR PHARMACOLOGIES

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Abstract – Novel triplet compounds with the 1,3-dioxa-5-thiazatriquinane and 1-oxa-3,5-dithiazatriquinane skeletons have been synthesized *via* the enantiomerically pure oxazoline intermediates. Their assay results showed that the substitution of sulfur atoms for the oxygen atoms increased the affinities for the opioid receptors and affected to the expression of the agonistic/antagonistic activities.

Since the discovery of the synthetic method for novel trimers with the 1,3,5-trioxazatriquinane skeleton,[1] we have reported many opioid receptor type-selective ligands with the trimer skeleton such as KNT-93 (**1**)[2] and KNT-123 (**2**)[3] (Figure 1). During those studies, we payed attention to the structure of the neurotransmitters which have a common structural moiety, phenethylamine (Figure 2). Focusing on the common structure, we also conceived some plausible structures which have one phenyl group (double capped trimer), two phenyl groups (mono capped trimer), or three phenyl groups (no capped trimer)[4] directly bound with the trimers skeleton as shown in Figure 3. On the basis of the common structural concept, a variety of trimer compounds bearing the phenethylamine-structure moiety depicted in Figure 3 were synthesized in the past decade. Intriguingly, the only mono capped trimer, SYK-146 (**3**)[4] strongly bound to κ opioid receptor (K_i = 4.63 nM for κ receptor, K_i >1,000 nM for μ and δ receptors) with almost

the same agonist activity as that of the standard κ agonist, U-69,593 (**4**)[5] for κ opioid receptor, although agonist **3** has a very simple structure, which was synthesized *via* only four steps from 3′-methoxyacetophenone.

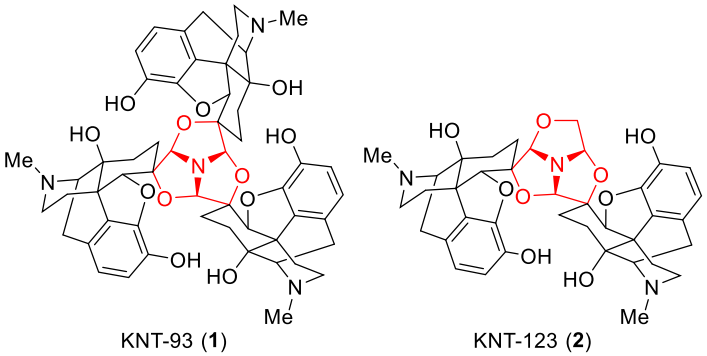


Figure 1. Structures of KNT-93 (**1**) and KNT-123 (**2**)

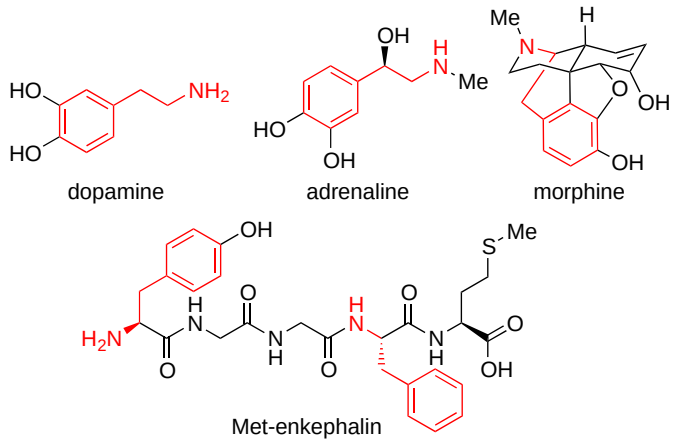


Figure 2. Common phenethylamine-structure of representative neurotransmitters

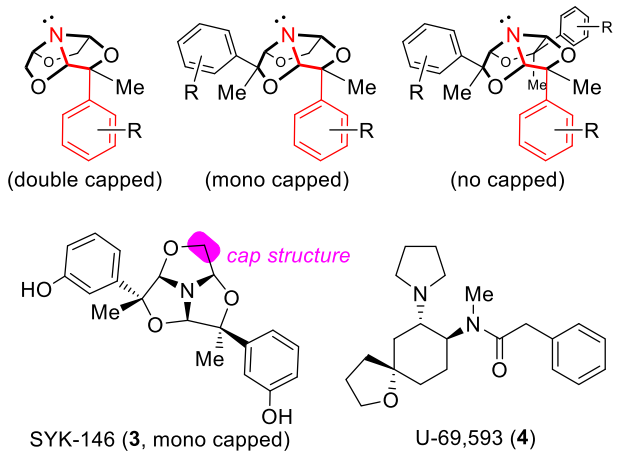
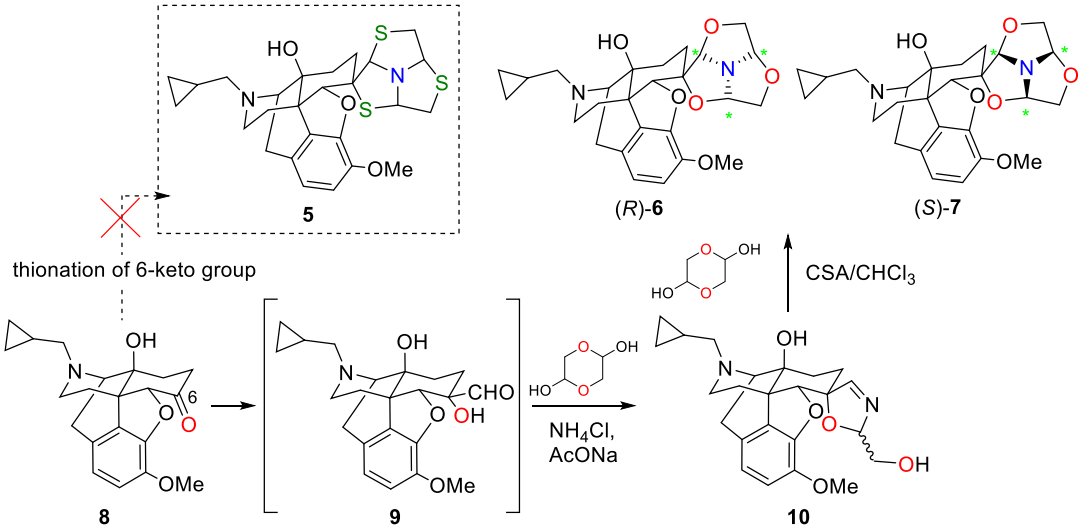


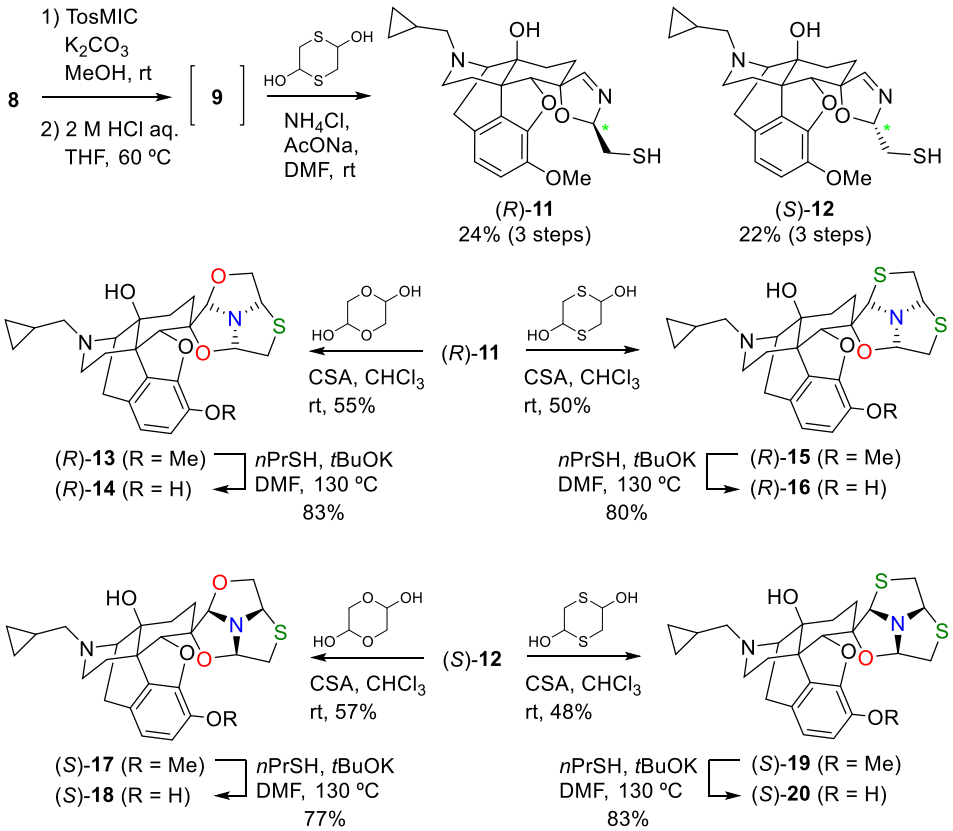
Figure 3. Conceptual diagram of trimers with the phenethylamine-structure and the structures of SYK-146 (**3**) and U-69,593 (**4**)

In the course of the above studies, we focused on the basicity of the nitrogen atom in the 1,3,5-trioxazatriquinane skeleton. The basicity of the trimers was found to be extremely weak compared to that of general tertiary amine (triethylamine) calculated with ADMET Predictor,[6] because of the strong electron withdrawing abilities of the three oxygen atoms in the trimer skeleton. Many researchers believe that the ion interaction derived from the basic nitrogen, not only in the opioid derivatives, but also in other neurotransmitters, should be the most important pharmacophore for the corresponding receptors. Thus, the lower basicity of nitrogen is predicted to lower the affinities of the ligands. In fact, we reported that the reduction of the basicity of the nitrogen functional group by the introduction of fluorine atoms to the 17 position in the morphinan skeleton led to weaker affinity for the opioid receptors.[7] Furthermore, we predicted the affinity-change of the trimer compounds for opioid receptors, based on the difference of the bond length from the O–C bond (143 pm) to S–C bond (182 pm) in the trimer skeleton.[8]

At first, we attempted to replace three oxygen atoms with three sulfur atoms on the double capped trimer **5** bearing a morphinan skeleton by utilizing the same synthetic method as for the known double capped trimers (*R*)-**6** and (*S*)-**7** *via* the hydroxymethyl oxazoline intermediate **10**[9] (Scheme 1). However, our many trials to convert the 6-keto group into the corresponding 6-thioketo group of naltrexone methyl ether (**8**) were in vain because of the instability of the resulting thioketone.[10] The results inevitably led us to synthesize the double capped trimers with one sulfur atom or two sulfur atoms as shown in Scheme 2. Naltrexone methyl ether (**8**) was treated with *p*-toluenesulfonylmethyl isocyanide (TosMIC)[12] in the presence of K_2CO_3, and then 2 M HCl aq. to afford the α-hydroxyaldehyde **9**. Without any purification of the obtained **9**, it was converted into the mercaptomethyl oxazoline intermediates (*R*)-**11** and (*S*)-**12** by the treatment with 1,4-dithiane-2,5-diol in 24% and 22% yields from **8**, respectively. The reactions of (*R*)-**11** and (*S*)-**12** with glycolaldehyde dimer afforded the 1,3-dioxa-5-thiazatriquinane compounds (*R*)-**13** and (*S*)-**17**, respectively. On the other hand, the reactions of (*R*)-**11** and (*S*)-**12** with 1,4-dithiane-2,5-diol afforded the 1-oxa-3,5-dithiazatriquinane compounds (*R*)-**15** and (*S*)-**19**, respectively. Those stereochemistries of the methine moieties of trimer compounds (*R*)-**13**, (*R*)-**15**, (*S*)-**17**, and (*S*)-**19** were determined by the NOESY experiments depicted in Figure 4. *O*-Demethylation of (*R*)-**13**, (*R*)-**15**, (*S*)-**17**, and (*S*)-**19** was conducted by treatment with *n*PrSH and *t*BuOK to give the corresponding phenolic compounds (*R*)-**14**, (*R*)-**16**, (*S*)-**18**, and (*S*)-**20**.



Scheme 1. Previous synthesis of the double capped 1,3,5-trioxazatriquinane compounds (*R*)-**6** and (*S*)-**7** and the initial attempt to synthesize 1,3,5-trithiazatriquinane compounds **5**



Scheme 2. Synthesis of the double capped trimers, 1,3-dioxa-5-thiazatriquinane compounds (*R*)-**14** and (*S*)-**18** and 1-oxa-3,5-dithiazatriquinane compounds (*R*)-**16** and (*S*)-**20**

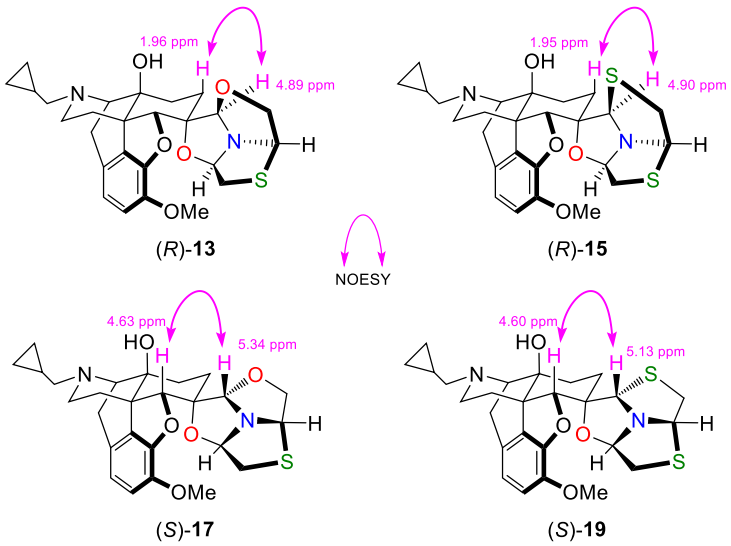
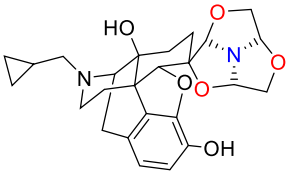


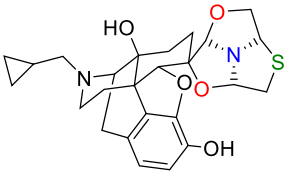
Figure 4. Observed NOESY correlations in the trimer compounds (*R*)-**13**, (*R*)-**15**, (*S*)-**17**, and (*S*)-**19**

Next, we evaluated the binding affinities and agonistic activities of the obtained compounds (*R*)-**14**,[13] (*R*)-**16**,[14] (*S*)-**18**,[15] and (*S*)-**20**[16] for the opioid receptors in the opioid receptor binding assay and the [^{35}S]GTPγS-binding assay. The assays were performed by a previously reported procedure[9] and those results were shown in Table 1. As we expected, the affinities of most of the thio-derivatives for the opioid receptors were increased compared with those of the double capped 1,3,5-trioxazatriquinane compounds SYK-134 ((*R*)-**21**) and SYK-135 ((*S*)-**22**), which were derived from (*R*)-**6** and (*S*)-**7** by demethylation, respectively.[9] The μ/κ selective ratios of all the thio-compounds were decreased. On the other hand, the δ/κ ratios of the *R* isomers were improved, in contrast to the case of *S* isomers. These results showed that the affinities for μ opioid receptor were more influenced than those for κ opioid receptor by the introduction of the sulfur atoms. The most impressive result was the participation of the sulfur atoms in the trimer skeleton to express the agonistic activity. That is, although SYK-134 ((*R*)-**21**) showed the agonistic activity for the κ opioid receptor, the (*R*)-**14** with one sulfur atom and (*R*)-**16** with two sulfur atoms showed antagonistic activity for μ and κ opioid receptors (Table 1). In contrast, although SYK-135 ((*S*)-**22**) showed antagonistic activity for μ and κ opioid receptors, (*S*)-**18** and (*S*)-**20** showed partial agonistic activities for the μ and δ receptors, respectively (Table 1). It is not clear that these changes in the activities could be derived from the differences of the electron density on the central nitrogen or the bond length between the oxygen and sulfur atoms. In the near future, we will seek to clarify the reason through the synthesis of simpler mono-capped and double-capped trimer derivatives with a sulfur atom and the evaluation of their pharmacological effects.

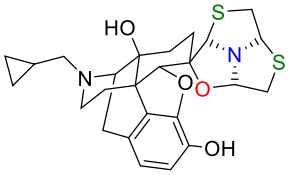
Table 1. Pharmacological binding properties of the synthesized double capped trimers for opioid receptors



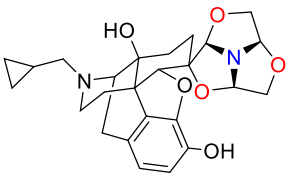
SYK-134 ((*R*)-**21**)
agonistic activity
EC_{50} (κ) = 25.0 nM, E_{max} (κ) = 70.0%



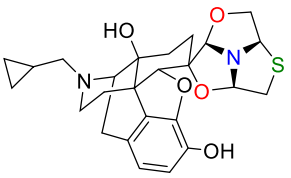
(*R*)-**14**
antagonistic activity
IC_{50} (μ) = 148 nM
IC_{50} (κ) = 453 nM



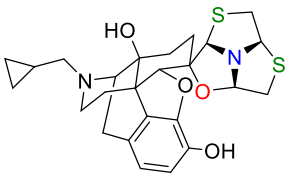
(*R*)-**16**
antagonistic activity
IC_{50} (μ) = 68.6 nM
IC_{50} (κ) = 555 nM



SYK-135 ((*S*)-**22**)
antagonistic activity
IC_{50} (μ) = 133 nM
IC_{50} (κ) = 543 nM



(*S*)-**18**
agonistic activity
EC_{50} (μ) = 0.97 nM, E_{max} (μ) = 38.7%



(*S*)-**20**
agonistic activity
EC_{50} (δ) = 63.0 nM, E_{max} (δ) = 68.2%

Compounds	K_i (nM)			Selectivity	
	μ	δ	κ	μ/κ	δ/κ
(*R*)-**21**[a]	8.65	99.8	3.86	2.24	25.9
(*R*)-**14**	2.78	60.9	1.41	1.97	43.2
(*R*)-**16**	2.69	248	1.94	1.39	128
(*S*)-**22**[a]	6.85	78.6	5.95	1.15	13.2
(*S*)-**18**	3.23	26.0	3.21	1.00	8.10
(*S*)-**20**	1.96	17.1	9.08	0.21	1.88

[a] The data of (*R*)-**21** and (*S*)-**22** were tested in the previous work.[9]

In conclusion, we synthesized novel 1,3-dioxa-5-thiazatriquinane and 1-oxa-3,5-dithiazatriquinane derivatives *via* the key oxazoline intermediates (*R*)-**11** or (*S*)-**12** with the methanethiol group and evaluated their binding affinities and agonistic/antagonistic activities for the opioid receptors. The assays showed that the substitution of the sulfur atoms for the oxygen atoms increased the affinities for the opioid receptors and affected the expression of the agonistic activities. To the best of our knowledge, the effect of the sulfur atom in the trimer skeleton on the expression of the agonistic activity has not reported. This work is expected to be helpful for many medicinal chemists designing new drugs.

ACKNOWLEDGEMENTS

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13. Compound (*R*)-**14**: Colorless amorphous material. IR (film, cm^{-1}): 2925, 1616, 1462, 1339, 1253, 1102. ^1H NMR (400 MHz, $CDCl_3$): δ 0.08–0.16 (m, 2H), 0.47–0.56 (m, 2H), 0.79–0.88 (m, 1H),

1.43–1.57 (m, 3H), 1.72 (ddd, *J* = 14.6, 4.2, 4.2 Hz, 1H), 1.94 (ddd, *J* = 14.3, 11.0, 4.2 Hz, 1H), 2.15–2.29 (m, 2H), 2.33–2.39 (m, 2H), 2,56 (dd, *J* = 18.3, 6.0 Hz, 1H), 2.65 (d, *J* = 8.7 Hz, 1H), 2.99 (d, *J* = 18.3 Hz, 1H), 3.05–3.12 (m, 1H), 3.23 (dd, *J* = 12.4, 4.2 Hz, 1H), 3.37 (dd, *J* = 12.4, 1.8 Hz, 1H), 3.69 (dd, *J* = 10.0, 3.2 Hz, 1H), 3.96 (d, *J* = 10.0 Hz, 1H), 4.72 (s, 1H), 4.85 (s, 1H), 4.92 (d, *J* = 3.2 Hz, 1H), 5.06 (dd, *J* = 3.6, 1.8 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H). The two OH peaks were not observed. ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.9, 4.1, 9.5, 22.7, 27.1, 27.4, 31.7, 36.8, 44.2, 48.0, 59.3, 62.4, 69.9, 72.1, 80.2, 85.6, 89.8, 94.3, 101.0, 117.2, 118.8, 123.8, 130.4, 138.3, 145.6. HR-MS (ESI): *m*/*z* $[M+H]^+$ Calcd for $C_{25}H_{31}N_2O_5S$: 471.1954. Found: 471.1956.

14. Compound (*R*)-**16**: Colorless amorphous material. IR (film, cm^{-1}): 2927, 1621, 1458, 1237, 1100. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07–0.18 (m, 2H), 0.56–0.62 (m, 2H), 0.78–0.90 (m, 1H), 1.45 (ddd, *J* = 13.7, 4.1, 4.1 Hz, 1H), 1.49–1.58 (m, 2H), 1.69 (ddd, *J* = 14.2, 4.1, 4.1 Hz, 1H), 1.90 (ddd, *J* = 14.2, 11.5, 4.1 Hz, 1H), 2.19 (ddd, *J* = 11.9, 11.9, 3.6 Hz, 1H), 2.28 (ddd, *J* = 12.0, 12.0, 5.0 Hz, 1H), 2.33–2.41 (m, 2H), 2.57 (dd, *J* = 18.2, 6.0 Hz, 1H), 2.66 (dd, *J* = 10.0, 4.1 Hz, 1H), 2.99 (d, *J* = 18.4 Hz, 1H), 3.07–3.12 (m, 2H), 3.20 (dd, *J* = 5.0, 5.0 Hz, 1H), 3.23 (dd, *J* = 5.0, 5.0 Hz, 1H), 3.31 (dd, *J* = 11.7, 5.4 Hz, 1H), 4.66 (s, 1H), 4.90 (s, 1H), 4.95 (dd, *J* = 5.4, 5.4 Hz, 1H), 4.98 (dd, *J* = 5.0, 2.3 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H). The two OH peaks were not observed. ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.9, 4.1, 9.4, 22.7, 27.4, 27.5, 31.5, 38.0, 38.6, 44.3, 47.9, 59.3, 62.4, 69.9, 75.2, 80.0, 85.8, 90.2, 96.8, 117.1, 118.7, 124.0, 130.6, 138.1, 145.7. HR-MS (ESI): *m*/*z* $[M+H]^+$ Calcd for $C_{25}H_{31}N_2O_4S_2$: 487.1725. Found: 487.1711.

15. Compound (*S*)-**18**: Colorless amorphous material. IR (film, cm^{-1}): 2925, 1616, 1462, 1247, 1102. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06–0.16 (m, 2H), 0.49–0.56 (m, 2H), 0.78–0.86 (m, 1H), 1.47 (d, *J* = 11.0 Hz, 1H), 1.58–1.80 (m, 3H), 1.97 (ddd, *J* = 14.8, 8.0, 8.0 Hz, 1H), 2.15–2.29 (m, 2H), 2.30–2.40 (m, 2H), 2.57–2.66 (m, 2H), 3.01 (d, *J* = 18.8 Hz, 1H), 3.11 (d, *J* = 6.0 Hz, 1H), 3.27 (d, *J* = 12.8 Hz, 1H), 3.31 (dd, *J* = 12.8, 3.2 Hz, 1H), 3.69 (dd, *J* = 10.0, 3.6 Hz, 1H), 3.97 (d, *J* = 10.0 Hz, 1H), 4.65 (s, 1H), 5.06 (d, *J* = 2.8 Hz, 1H), 5.39 (d, *J* = 3.6 Hz, 1H), 5.41 (s, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H). The two OH peaks were not observed. ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.8, 4.2, 9.5, 22.6, 25.7, 28.8, 33.0, 37.9, 43.8, 48.2, 59.4, 62.4, 69.5, 71.5, 80.5, 86.2, 92.7, 96.7, 100.3, 117.6, 119.1, 125.0, 130.9, 137.7, 144.6. HR-MS (ESI): *m*/*z* $[M+H]^+$ Calcd for $C_{25}H_{31}N_2O_5S$: 471.1954. Found: 471.1958.

16. Compound (*S*)-**20**: Colorless amorphous material. IR (film, cm^{-1}): 2927, 1620, 1457, 1237. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.05–0.18 (m, 2H), 0.47–0.58 (m, 2H), 0.79–0.88 (m, 1H), 1.46 (d, *J* = 9.2 Hz, 1H), 1.58–1.72 (m, 2H), 1.80 (ddd, *J* = 14.0, 6.0, 6.0 Hz, 1H), 2.08 (ddd, *J* = 13.6, 8.2, 5.5 Hz, 1H), 2.15–2.27 (m, 2H), 2.30–2.40 (m, 2H), 2.56–2.65 (m, 2H), 2.98–3.12 (m, 4H), 3.15 (dd, *J* = 12.4, 2.8 Hz, 1H), 3.45 (dd, *J* = 12.4, 5.3 Hz, 1H), 4.62 (s, 1H), 4.92 (dd, *J* = 5.0, 2.8 Hz, 1H), 5.19 (s, 1H),

5.44 (dd, *J* = 4.6, 4.6 Hz, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H). The two OH peaks were not observed. ^{13}C NMR (100 MHz, $CDCl_3$): δ 3.87, 4.14, 9.48, 22.6, 26.5, 28.5, 32.6, 38.0, 40.9, 43.9, 48.0, 59.4, 62.4, 69.6, 74.0, 81.0, 87.3, 93.2, 100.5, 117.5, 119.0, 124.6, 130.8, 137.8, 144.7. HR-MS (ESI): *m*/*z* $[M+H]^+$ Calcd for $C_{25}H_{31}N_2O_4S_2$: 487.1725. Found: 487.1731.