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Dehydrative Cyclization Catalyzed by the Combination of Molybdenum(VI) Oxides and Benzoic Acids: First Synthesis of the Antitumour Substance BE-70016

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Dedicated to Prof. M. Shibasaki on the occasion of his 60th birthday.

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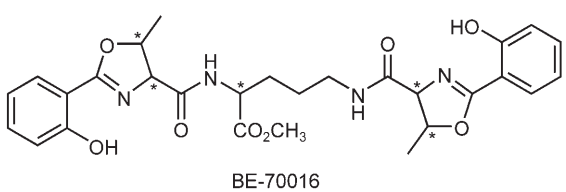
Abstract: The dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivative **1a** is efficiently promoted by the combined use of molybdenum(VI) oxides and benzoic acids bearing electron-withdrawing substituents. In the presence of ammonium molybdate [$(NH_4)_2MoO_4$, 10 mol%] and pentafluorobenzoic acid ($C_6F_5CO_2H$; 10 mol%), dehydrative cyclization of **1a** was conducted in toluene under azeotropic reflux conditions to give 2-(*o*-hydroxyphenyl)oxazoline **2a** in 76% yield. Furthermore, the first total synthesis of the antitumour substance BE-70016 was achieved using the catalytic dehydrative cyclization of **1a** as a key reaction.

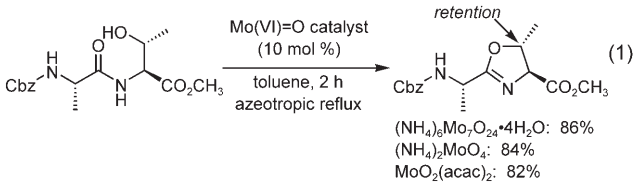
Keywords: catalysis; dehydrative cyclization; molybdenum(VI) oxide; oxazolines; pentafluorobenzoic acid

Since the late 1980s, many oxazoline-containing natural products have been isolated from marine organisms.[1] The biosynthesis of these oxazolines appears to involve the dehydrative cyclization of serine and threonine residues.[1c] Among these oxazoline-containing natural compounds, 2-(*o*-hydroxyphenyl)oxazoline structures are often found. For example, BE-70016 is an antitumour substance that was isolated from *Actinoplanes* sp.[2] This compound appears to be useful in the control of human and mouse tumours. These 2-(*o*-hydroxyphenyl)oxazoline-containing natural products are generally considered to be siderophores,[3] which are defined as low molecular weight, Fe(III)-specific transport agents. These compounds are thought to be derived from *N*-(*o*-hydroxybenzoyl)threonine.



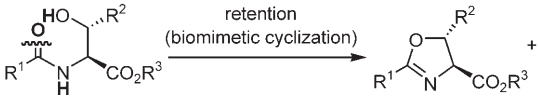
BE-70016

Although several stoichiometric reagents are known to be effective for the chemical dehydrative cyclization of serine and threonine residues,[4] few successful examples of dehydrating catalysts have been reported.[5] Recently, we reported molybdenum(VI) oxides as highly effective dehydrative cyclization catalysts for the synthesis of oxazolines and thiazolines [Eq. (1)].[6]

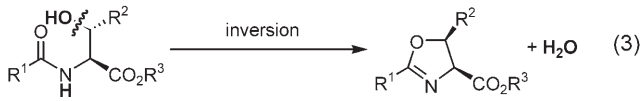


(1)

There are two known methodologies for the chemical synthesis of oxazolines: the retentive cyclization of *N*-acylthreonine derivatives at the β-position (biomimetic cyclization) [Eq. (2)], and its invertive cyclization [Eq. (3)]. As in biosynthesis, the molybdenum oxide-catalyzed dehydrative cyclization of threonine derivatives proceeds with retention of configuration at the β-position, while most reactions that use stoichiometric dehydrating reagents proceed with inversion of configuration at the β-position.[4b–g,i,j] Therefore, the molybdenum oxide-catalyzed method [Eq.



(2)

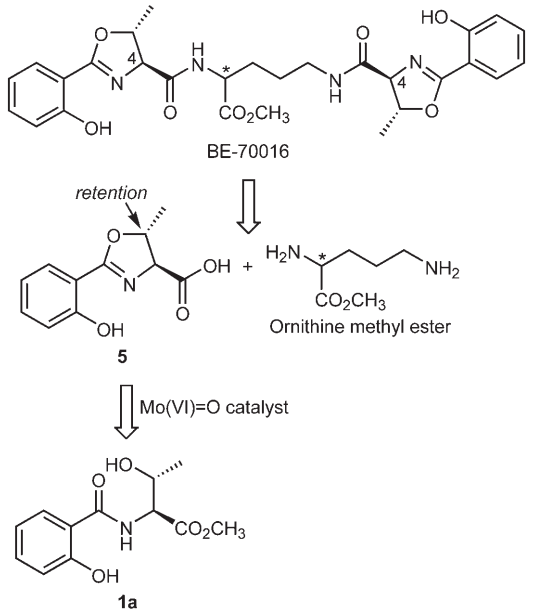


(3)

(1)] is quite useful for the synthesis of naturally occurring oxazolines derived from an L-threonine residue. When we synthesize L-threonine-derived oxazolines using stoichiometric dehydrating reagents,[7,8] L-*allo*-threonine, which is much more expensive than L-threonine, is needed.

We report here the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine derivative **1a** catalyzed by the combination of molybdenum(VI) oxides and benzoic acids bearing electron-withdrawing substituents. Furthermore, we have achieved the first total synthesis of BE-70016 using the molybdenum oxide-catalyzed dehydrative cyclization as a key reaction.

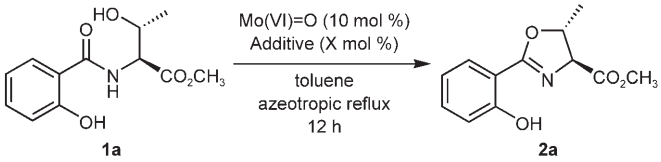
Scheme 1 shows a retrosynthesis of BE-70016. This compound is composed of two molecules of salicylic acid, two molecules of threonine, and one molecule of ornithine. We planned to synthesize BE-70016 biomimetically by the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)threonine methyl ester[9] followed by condensation with ornithine methyl ester. Although the relative and absolute stereochemistries of natural BE-70016 are not shown in the original patent,[2] we considered that the relative stereochemistries of the two oxazoline rings were *trans* based on the coupling constants of protons at the 4-positions of the oxazoline rings [$\delta = 4.39$ (d, $J = 7.6$ Hz, 1H) and 4.43 (d, $J = 7.6$ Hz, 1H)].[5g] Amide condensation between 4-oxazolinecarboxylic acid **3** and both enantiomers of ornithine methyl esters would give two possible diastereomers of BE-70016. The absolute stereochemistry of BE-70016 would be determined based on a comparison of the sense of the optical rotation. It was expected that compound **3** could be prepared from L-threonine by molybdenum oxide-catalyzed dehydrative cyclization with a retention of configuration at the β-position.



Scheme 1. Retrosynthesis of BE-70016.

We initially investigated the dehydrative cyclization of **1a** to **2a** using molybdenum(VI) oxides as catalysts (Table 1). Compound **2a** is one of the most important common intermediates for the synthesis of many oxazoline-containing bioactive natural products. The development of an efficient and practical method for the synthesis of this compound is strongly needed. Unfortunately, however, the catalytic activities of $(NH_4)_2MoO_4$ and $MoO_2(acac)_2$ for the dehydrative cyclization of **1a** were very low (entries 1 and 2), although they show excellent catalytic activities for the reaction of Cbz-L-Ala-L-Thr-OCH_3 [see Eq. (1)].[6] To

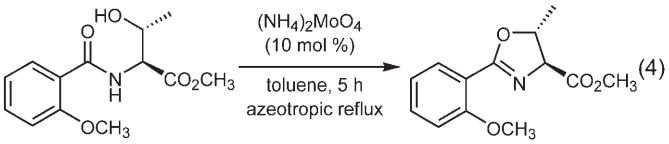
Table 1. Dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-threonine methyl ester (**1a**).[a]



Entry	Mo(VI)=O	Additive	X [mol %]	Yield[b] [%]
1	$(NH_4)_2MoO_4$	-	-	17
2	$MoO_2(acac)_2$	-	-	5
3	$(NH_4)_2MoO_4$	TsOH	10	19
4	$(NH_4)_2MoO_4$	$C_6H_5CO_2H$	10	57[c]
5	$(NH_4)_2MoO_4$	$C_6F_5CO_2H$	2	47[d]
6	$(NH_4)_2MoO_4$	$C_6F_5CO_2H$	10	76
7	$(NH_4)_2MoO_4$	$C_6F_5CO_2H$	20	76
8	$(NH_4)_2MoO_4$	3,5-$(CF_3)_2C_6H_3CO_2H$	10	76
9	$(NH_4)_2MoO_4$	4-$(NO_2)C_6H_4CO_2H$	10	67
10	$MoO_2(acac)_2$	$C_6F_5CO_2H$	10	76[c]
11	$MoO_2(acac)_2$	3,5-$(CF_3)_2C_6H_3CO_2H$	10	79
12	-	TsOH	10	19
13	-	$C_6F_5CO_2H$	10	1
14	-	3,5-$(CF_3)_2C_6H_3CO_2H$	10	0

[a] The reaction of **1a** (1 mmol) was conducted in toluene (10 mL) under azeotropic reflux conditions.
[b] Evaluated by ^1H NMR analysis.
[c] The reaction was conducted for 10 h.
[d] The reaction was conducted for 11 h.

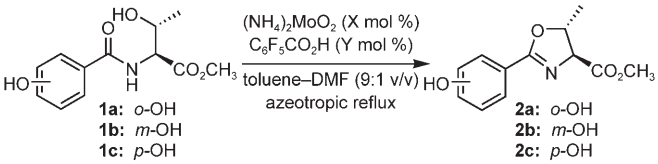
increase the reactivity, we examined several Brønsted acids as additives. *p*-Toluenesulfonic acid (TsOH) did not promote the reaction of **1a** (entry 3). The catalytic activity of TsOH itself was also very low (entry 12), although it shows good catalytic activity for the dehydrative cyclization of *N*-(*p*-methoxybenzoyl)-L-threonine methyl ester.[5g] Very interestingly, some benzoic acids bearing electron-withdrawing substituents efficiently promoted the molybdenum(VI) oxide-catalyzed dehydrative cyclization of **1a**. In particular, pentafluorobenzoic acid ($C_6F_5CO_2H$), 3,5-bis(trifluoromethyl)benzoic acid [3,5-$(CF_3)_2C_6H_3CO_2H$] and 4-nitrobenzoic acid [4-$(NO_2)C_6H_4CO_2H$] gave excellent results (entries 4, 6 and 8–11). In the presence of $(NH_4)_2MoO_4$ (10 mol%) and $C_6F_5CO_2H$ (10 mol%), a solution of **1a** was heated under azeotropic reflux conditions with the removal of water for 12 h. After aqueous work-up (washing with a 1 M aqueous solution of citric acid), oxazoline **2a** was obtained in 76% yield. Since these benzoic acids themselves showed very low catalytic activities (entries 13 and 14), they primarily promoted the activities of molybdenum(VI) oxides. The optimized amount of benzoic acid was 1 mol equiv. per molybdenum(VI) oxide (entries 5–7). One of the reasons for the low catalytic activities of molybdenum(VI) oxides is the tight complexation of molybdenum(VI) oxide with **2a**. Actually, the reaction of *N*-(*o*-methoxybenzoyl)-L-threonine methyl ester (**3**) proceeded well even in the absence of benzoic acids to give oxazoline **4** in 75% yield [Eq. (4)]. Benzoic acids might promote decomposition of the stable and inactivated complexes to regenerate the active molybdenum(VI) oxide species. The experimental result that the isolated yield of **2a** was decreased without an aqueous work-up also supported the formation of stable complexes of the molybdenum(VI) oxide with **2a**.



3 **4**: 75% (4)

Next, we examined the dehydrative cyclization of *m*- and *p*-hydroxy derivatives **1b** and **1c** (Table 2). Since **1b** and **1c** did not dissolve in toluene, the reaction was conducted in toluene-DMF (9:1, v/v). When the reaction of **1c** was conducted in the presence of $(NH_4)_2MoO_4$ (10 mol%) and $C_6F_5CO_2H$ (10 mol%), the corresponding oxazoline **2c** was obtained in 88% yield (entry 1). Interestingly, in contrast to the reaction of **1a**, the reactions of **1c** and **1b** proceeded smoothly in the absence of pentafluorobenzoic acid, to give **2c** and **2b** in respective yields of 87 and 91%

Table 2. Dehydrative cyclization of *m*- and *p*-hydroxy derivatives **1b** and **1c**.[a]



1a: *o*-OH **1b**: *m*-OH **1c**: *p*-OH — **2a**: *o*-OH **2b**: *m*-OH **2c**: *p*-OH

Entry	Substrate	$(NH_4)_2MoO_4$ [mol%]	$C_6F_5CO_2H$ [mol%]	Time [h]	Yield [%][b]
1	**1c**	10	10	2	88
2	**1c**	2	0	4	87
3	**1b**	2	0	1	91
4	**1a**	10	10	10	18

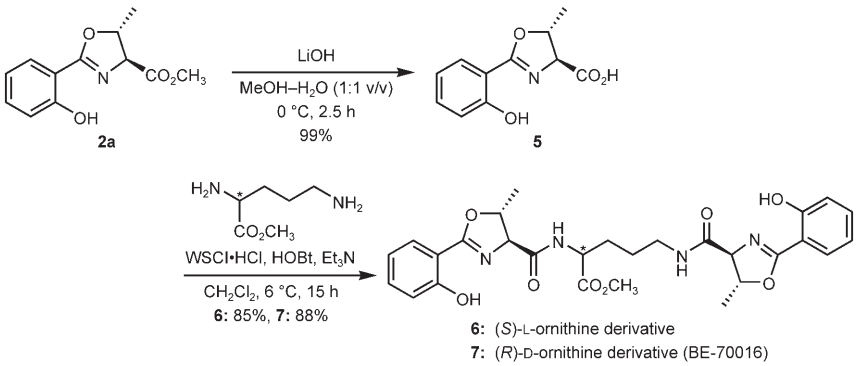
[a] The reaction of **1b** or **1c** (1 mmol) was conducted in toluene-DMF (9:1,v/v, 10 mL) under azeotropic reflux conditions.

[b] Evaluated by ^{1}H NMR analysis.

(entries 2 and 3). Only 2 mol% of the catalyst was sufficient to obtain the products in good yields. The coordination of the oxazolyl nitrogen of **2a** and **2c** to molybdenum(VI) oxides should be stronger than that of **2b** due to the resonance effect of the hydroxy group at the *o*- and *p*-positions. The higher reactivity of **1b** compared to those of **1a** and **1c** can be explained by the faster release of **2b** from the catalyst compared to **2a** and **2c**. Since **2a** was obtained in 18% yield when the reaction of **1a** catalyzed by $(NH_4)_2MoO_4$ and $C_6F_5CO_2H$ was conducted in toluene-DMF (9:1, v/v) (entry 4), DMF did not promote the reaction. A highly polar solvent such as DMF was not suitable for **1a** which was soluble in toluene.[6]

With the key intermediate (**2a**) for the synthesis of BE-70016 in hand, we investigated the synthesis of BE-70016 (Scheme 2). Hydrolysis of **2a** with lithium hydroxide gave carboxylic acid **5** in quantitative yield. The condensation of ornithine methyl esters was conducted with **5** (3.0 mol equivs.) using WSCI·HCl (3.0 mol equivs.) and HOBt (2.0 mol equivs.) in CH_2Cl_2, to give (*S*)-L-ornithine derivative **6** and (*R*)-D-ornithine derivative **7** in respective yields of 85 and 88%. As shown in Table 3, some signals in the ^{1}H NMR spectra of **6** were obviously different from those of natural BE-70016 and **7**. Based on a comparison of IR, ^{1}H and ^{13}C NMR, HRMS and specific rotation ($[\alpha]_D$), **7** was found to be identical to natural BE-70016. Thus, we have elucidated the stereochemical structure of BE-70016 as depicted in formula **7**, which was composed of salicylic acid, L-threonine and unnatural D-ornithine. Furthermore, we have achieved the first total synthesis of BE-70016 using the retentive cyclization of **1a** as a key reaction.

In conclusion, we have succeeded in the catalytic dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-threonine derivatives without protecting the *o*-hy-



Scheme 2. Synthesis of BE-70016.

Table 3. Selected spectral data of natural BE70016, and synthetic products **6** and **7**.

	Natural BE-70016	**6**	**7**	
^{1}H NMR [ppm]	1.76	1.72	1.76	m, 1H (β-position of ornithine)
	3.33	3.20	3.33	m, 1H (δ-position of ornithine)
	3.69	3.76	3.69	s, 3H (methyl ester)
$[\alpha]_D$	+10.3	+1.6	+10.6	

droxy group. The reaction was efficiently promoted by the combination of molybdenum(VI) oxides and benzoic acids bearing electron-withdrawing substituents, such as $C_6F_5CO_2H$. Furthermore, we have achieved the first total synthesis of the antitumor substance BE-70016 *via* a biomimetic strategy using molybdenum(VI) oxide-catalyzed dehydrative cyclization as a key reaction. The present strategy may be suitable for the efficient and practical synthesis of several bioactive natural products containing 2-(*o*-hydroxyphenyl)oxazolines.

Experimental Section

Preparation of Methyl (4*S*,5*R*)-2-(*o*-Hydroxyphenyl)-5-methyl-4-oxazolinecarboxylate (2a)

A solution of **1a** (253 mg, 1 mmol), $(NH_4)_2MoO_4$ (20 mg, 0.10 mmol) and $C_6F_5CO_2H$ (21 mg, 0.10 mmol) in toluene (10 mL) was heated at azeotropic reflux with the removal of water using a Dean–Stark apparatus. After 12 h, the reaction mixture was cooled to ambient temperature, diluted with EtOAc (10 mL) and washed with 1 M citric acid in saturated aqueous NaCl (15 mL), saturated aqueous $NaHCO_3$ and NaCl (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4 and concentrated to give a crude product. Yields were determined by HPLC analysis or ^{1}H NMR analysis. The crude product was purified by column chromatography on silica gel using a mixture of hexane-EtOAc (15:1→13:1→10:1) as an eluent to give **2a**: colorless oil; IR (neat): ν = 1743, 1638, 1614, 1491, 1438, 1355, 1310, 1259, 1229, 1207, 1157, 1134, 1072, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (d, J = 6.3 Hz, 3H), 3.80 (s, 3H), 4.50 (d, J = 6.9 Hz, 1H), 4.98 (qd, J = 6.3, 6.9 Hz, 1H), 6.87 (ddd, J = 0.9, 7.2, 7.8 Hz, 1H), 7.01 (dd, J = 0.9, 8.4 Hz, 1H), 7.39 (ddd, J = 1.5, 7.2, 8.4 Hz, 1H), 7.66 (dd, J = 1.5, 7.8 Hz, 1H), 11.8 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 52.8, 73.7, 78.5, 110.4, 117.0, 118.8, 128.4, 134.0, 160.1, 167.0, 171.0; HR-MS (FAB): m/z = 236.0925, calcd. for $C_{12}H_{14}NO_4$ $[M+H]^+$: 236.0923.

Preparation of (4*S*,5*R*)-2-(*o*-Hydroxyphenyl)-5-methyl-4-oxazolinecarboxylic Acid (5)

To a solution of **2a** (588 mg, 2.5 mmol) in methanol (10 mL) was added a 1.0 M aqueous solution of LiOH (10 mL, 10 mmol) at ambient temperature, and the mixture was stirred for 2.5 h. The reaction mixture was cooled to 0 °C and acidified (pH 2) with concentrated aqueous HCl. After MeOH was removed under vacuum, the resulting aqueous layer was extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated, to give **5** as a colorless amorphous powder; yield: 550 mg (99 %); IR (KBr): ν = 1732, 1637, 1491, 1446, 1372, 1308, 1259, 1158, 1133, 1073, 1037 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (d, J = 6.3 Hz, 3H), 4.39 (d, J = 7.5 Hz, 1H), 4.93 (qd, J = 6.3, 7.5 Hz, 1H), 6.78 (dd, J = 7.8, 8.4 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.4, 8.4 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 11.8 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7, 73.5, 78.4, 110.3, 116.8, 118.4, 128.2, 133.6, 160.1, 166.6, 171.6; HR-MS (FAB): m/z = 222.0772, calcd. for $C_{11}H_{12}NO_4$ $[M+H]^+$: 222.0766.

Preparation of BE-70016 (7)

To a solution of **2a** (465 mg, 2.1 mmol), (*R*)-ornithine methyl ester·2 HCl (153 mg, 0.70 mmol), HOBt (189 mg, 1.4 mmol) and Et_3N (195 μL, 1.4 mmol) in CH_2Cl_2 (10 mL) was added a solution of WSCI·HCl (403 mg, 2.1 mmol) and Et_3N (293 μL, 2.1 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After the mixture had been stirred at 6 °C for 15 h and then at ambient temperature for 2 h, CH_2Cl_2 was removed under vacuum and dissolved in EtOAc (50 mL). The resulting solution was washed with 1 M HCl (40 mL), saturated aqueous $NaHCO_3$ (2 × 40 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using a mixture of hexane-acetone (3:1→

2:1→1:1) as an eluent to give **7** as a colorless amorphous powder; yield: 340 mg (88%); IR (KBr): ν = 3352, 1743, 1668, 1637, 1613, 1523, 1490, 1445, 1372, 1350, 1310, 1258, 1227, 1157, 1134, 1074, 1039 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.60$ (d, $J = 6.5$ Hz, 3H), 1.62 (d, $J = 6.0$ Hz, 3H), 1.6–1.7 (m, 2H), 1.76 (m, 1H), 1.93 (dddd, $J = 5.5$, 8.5, 9.0, 14.0 Hz, 1H), 3.33 (ddd, $J = 6.5$, 7.0, 13.5 Hz, 1H), 3.38 (ddd, $J = 6.5$, 7.0, 13.5 Hz, 1H), 3.69 (s, 3H), 4.39 (d, $J = 7.5$ Hz, 1H) 4.43 (d, $J = 8.0$ Hz, 1H), 4.58 (dt, $J = 5.0$, 7.5 Hz, 1H), 4.84–4.93 (m, 2H), 6.67 (br s, 1H), 6.90 (ddd, $J = 1.0$, 7.5, 8.0 Hz, 2H), 6.91 (ddd, $J = 1.0$, 7.5, 8.0 Hz, 2H), 7.02 (m, 2H), 7.08 (br d, $J = 8.0$ Hz, 1H), 7.41 (ddd, $J = 1.0$, 7.5, 8.5 Hz, 1H), 7.42 (ddd, $J = 1.0$, 7.5, 8.5 Hz, 1H), 7.69 (dd, $J = 1.5$, 8.0 Hz, 1H), 7.69 (dd, $J = 1.5$, 8.0 Hz, 1H), 11.5 (br s, 1H), 11.5 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.7$, 21.8, 25.8, 29.7, 38.7, 51.8, 52.7, 74.3, 74.3, 79.4, 79.7, 110.4, 117.0, 117.1, 119.1, 119.2, 128.7, 128.7, 134.3, 134.3, 159.9, 160.0, 167.2, 167.5 170.7, 170.8, 172.0; HR-MS (FAB): $m/z =$ 553.2294, calcd. for $C_{28}H_{33}N_4O_8$ $[M+H]^+$: 553.2298.

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