JOC Article

Mild and Nonracemizing Conditions for Ullmann-type Diaryl Ether Formation between Aryl Iodides and Tyrosine Derivatives

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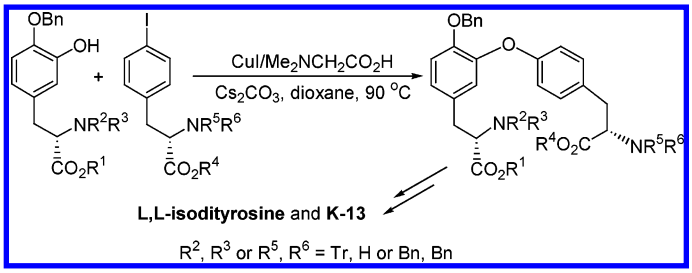


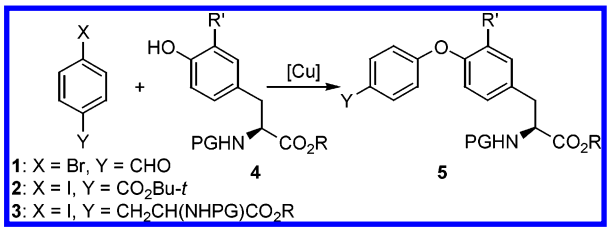
CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction of L-tyrosine derivatives and L-phenylalanine-derived iodides in the presence of Cs_2CO_3 works at 90 °C to provide the corresponding diaryl ether. Partial racemization occurs when N-Boc- and N-Cbz-protected aromatic amino esters are used, while N-trityl- and N,N-dibenzyl-protected aromatic amino esters give rise to coupling products without loss of optical purity. Little racemization is also observed in cases of N-Boc- and N-Cbz-protected aromatic amino acids as substrates. But their reaction yields are moderate. On the basis of these studies, shorter protocols for assembling (*S*,*S*)-isodityrosine and K-13 are developed.

Introduction

The Ullmann-type coupling reaction between aryl halides and protected tyrosine or related amino acid derivatives is an interesting subject because its products can be directly used for assembling a number of natural cyclopeptides bearing a diaryl ether moiety.[1] These compounds include monocyclic tripeptides such as K-13 and OF4949-I−IV, bicyclic bouvardins, and RP-664536, as well as complex polycyclic antibiotics such as vancomycin, teicoplanin, and chloropeptins.[1]

Since Ullmann-type diaryl ether formation is a well-established transformation process, a key problem for its application to tyrosine derivatives is how to avoid the possible racemization of their amino acid moiety. Indeed, the conventional reaction conditions (~170 °C) are almost certain to racemize amino acids. Initial attempts to couple two tyrosine derivatives under these conditions gave only 1.5% yield of the desired product.[2] In 1988 Schmidt et al.[3] reported that if

SCHEME 1



electron-deficient *p*-bromobenzaldehyde **1** (Scheme 1) was used, coupling with a tyrosine derivative **4** in the presence of CuO worked at 130 °C, affording the corresponding diaryl ether in good yield. Soon after that, Boger and Yohannes[4] and Rama Rao et al.[5] discovered that similar results could be obtained when two other electron-deficient aryl halides, *tert*-butyl *p*-iodobenzoate **2** and *p*-nitro-*m*-bromobenzaldehyde, were employed. However, coupling reactions between phenylalanine-derived aryl iodides **3** and tyrosine derivatives **4** failed to give any desired

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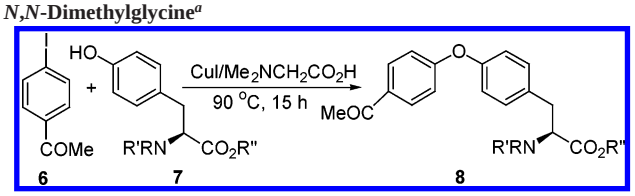
products.[6a] This problem might result from the poor reactivity of the aryl iodides **3**, which resulted in the need for a longer synthetic sequence for asymmetric elaboration of the required amino acid units in subsequent conversions to target molecules.[1,3−6]

Mild coupling reaction conditions could provide a solution to the above problem. Toward this goal, Nicolaou et al.[7] developed a synthetic technology in which a triazene unit was placed ortho to a leaving group on the aromatic ring to provide an ortho substitution effect. Through this modification they observed that the reaction between aryl halides and L-tyrosine derivatives proceeded smoothly at 80 °C. Recently, we[8a] and other groups[9,10] have revealed that some special ligands could promote Ullmann-type diaryl ether formation, leading to this transformation complete at 90−130 °C. By combination of the ligand effect and a newly discovered ortho substitution effect caused by the acetoamido groups, we found that CuI-catalyzed diaryl ether synthesis between L-phenylalanine-derived aryl halides and L-tyrosine derivatives took place at room temperature.[11] However, for completion of the target natural products, a drawback for Nicolaou's and our processes is the requirement to remove the N-containing ortho substituents or transform them into other functional groups via diazotization.[7,11] Consequently, a mild and nonracemizing method for coupling general L-phenylalanine-derived aryl halides and L-tyrosine derivatives is still required.

Results and Discussion

Since our reaction temperature for CuI/*N*,*N*-dimethylglycine-catalyzed coupling of aryl halides and phenols was relatively low,[8a] we envisaged that the asymmetric centers of some protected amino acids could be inert to these reaction conditions, thereby giving a chance to develop a useful method for coupling general L-phenylalanine-derived aryl halides and L-tyrosine derivatives. With this idea in mind, a reaction of 4-iodophenylacetone **6** with *N*-Boc-L-tyrosine methyl ester **7a** under the catalysis of CuI/*N*,*N*-dimethylglycine at 90 °C was conducted. As expected, coupling product **8a** was isolated in 92% yield (Table 1, entry 1). However, after measuring its rotation we disappointedly found that racemization had occurred almost completely. Using *N*-Cbz-L-tyrosine methyl ester **7b** gave a similar result (entry 2). To minimize the racemization, we attempted to reduce the dosage of Cs_2CO_3 to 0.6 equiv or employ less basic CsF as a base. In these cases improved results were observed, but partial racemization still took place as evidenced from moderate ee values determined (entries 3 and 4).

TABLE 1. Coupling of 4-Iodophenylacetone and L-Tyrosine Derivatives Catalyzed by 10 Mol % CuI and 30 Mol % *N*,*N*-Dimethylglycine[a]



entry	phenol	R	R′	R″	product	yield[b] (%)/ee[c] (%)
1	**7a**	Boc	H	Me	**8a**	92/6
2	**7b**	Cbz	H	Me	**8b**	88/6
3	**7a**	Boc	H	Me	**8a**	60/64[d]
4	**7a**	Boc	H	Me	**8a**	40/50[e]
5	**7c**	Tr	H	Me	**8c**	92/>99
6	**7d**	Bn	Bn	Me	**8d**	96/>97
7	**7e**	Bn	Me	Me	**8e**	86/>98
8	**7f**	Bn	H	Me	**8f**	70/>88
9	**7g**	Me	H	Me	**8g**	0/-
10	**7h**	Boc	H	H	**8a**	60/>97[f]
11	**7i**	Cbz	H	H	**8b**	53/>98[f]

[a] Reaction conditions: aryl iodide **6** (1 mmol), phenol **7** (1.5 mmol), CuI (0.1 mmol), *N*,*N*-dimethylglycine hydrochloride salt (0.3 mmol), Cs_2CO_3 (2.1 mmol), dioxane (2 mL), 90 °C, 15 h. [b] Isolated yield. [c] Ee value was determined by chiral HPLC. [d] Cs_2CO_3 (0.6 mmol) was used. [e] CsF (2.1 mmol) was used. [f] The product was isolated after esterification.

Considering that N-alkyl groups are poorer substituents for stabilizing adjacent carbanions compared with N-alkoxycarbonyl groups, we next tried to change the N-protecting groups of tyrosine to avoid the racemization. After some experimentation, it was found that *N*-trityl-L-tyrosine methyl ester **7c** gave the desired coupling product **8c** in 92% yield without any racemization (entry 5). Similar results were observed in cases of *N*,*N*-dibenzyl- and *N*-benzyl-*N*-methyl-l-tyrosine methyl esters (**7d** or **7e**) as the substrates (entries 6 and 7). However, partial racemization was noticed when *N*-benzyl-l-tyrosine methyl ester **7f** was used (entry 8), while *N*-methyl-l-tyrosine methyl ester **7g** gave no coupling product (entry 9). These results indicated that the bulkiness of the N-protecting groups also played a role in this reaction.

Reducing the stability of the carbanion by switching its neighboring alkoxycarbonyl to carboxylate groups is another possible approach to minimize the racemization. To this end, two N-protected amino acids **7h** and **7i** were checked under our standard reaction conditions. After coupling with 4-iodophenylacetone **6**, their products were treated with iodomethane to afford esters **8a** and **8b**, respectively. As expected, excellent ee values were determined for these two esters. However, the

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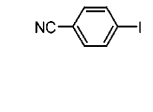
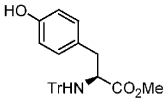
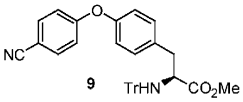
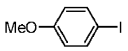
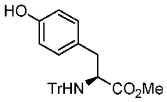
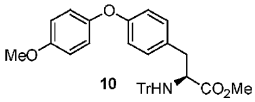
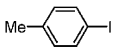
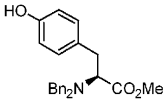
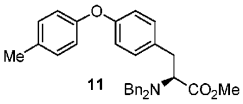
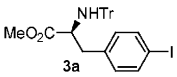
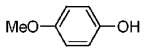
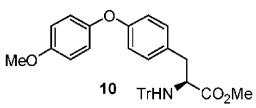
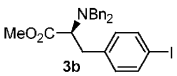
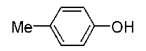
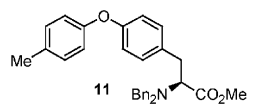
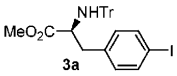
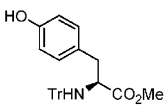
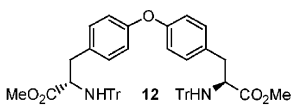
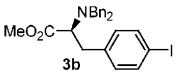
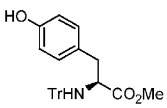
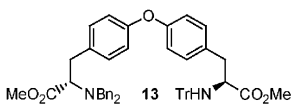
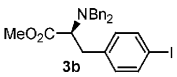
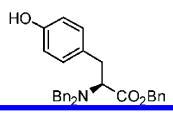
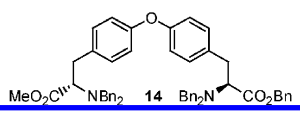
TABLE 2. Coupling Reaction of Aryl Iodides with L-Tyrosine Derivatives Catalyzed by 30 Mol % CuI and 100 Mol % *N,N*-Dimethylglycine[a]

entry	aryl iodide	phenol	time (h)	product	yield (%)[b] /ee (%)[c]
1			6	 **9**	90/95.2
2			6	 **10**	82/>99
3			6	 **11**	87/96.3
4	 **3a**		6	 **10**	88/>99
5	 **3b**		6	 **11**	77/97
6	 **3a**		22	 **12**	88/-[d]
7	 **3b**		22	 **13**	85/-[d]
8	 **3b**		22	 **14**	92/-[d]

[a] Reaction conditions: iodide (0.5 mmol), phenol (0.75 mmol), CuI (0.15 mmol), N,N-dimethylglycine hydrochloride salt (0.5 mmol), Cs_2CO_3 (1.5 mmol), dioxane (1 mL), 90 °C. [b] Isolated yield. [c] Ee value was determined by chiral HPLC. [d] Ee value was not determined.

overall yields were not satisfactory (entries 10 and 11), which implied that the presence of a carboxylate group in the substrates might slow the CuI-catalyzed coupling reaction.

On the basis of the above studies, we concluded that the best results could be obtained when N-trityl and N,N-dibenzyl (or N-benzyl for methylated amino acids) amino esters were utilized as the coupling substrates. To further explore the scope of this method, other related aryl iodides and phenols were examined. As summarized in Table 2, it was found that, besides electron-deficient iodides (entry 1), less reactive aryl iodides bearing an electron-donating group were also compatible with these reaction conditions (entries 2 and 3). This observation prompted us to test the coupling reaction with two phenylalanine-derived aryl iodides **3a** and **3b**. We were pleased that their reactions with simple phenols or even some tyrosine derivatives proceeded well, providing corresponding diaryl ethers in good yields (entries 4−8). Noteworthy is that, in products **13** and **14**, all amino and carboxylate groups have different protections, which would allow selective manipulation of individual functionalities in subsequent transformations.

To demonstrate the synthetic usage of the present method, we next attempted the total synthesis of two natural products via the CuI/*N,N*-dimethylglycine-catalyzed coupling reaction. The first molecule we studied was (*S,S*)-isodityrosine **19** (Scheme 2), a naturally occurring amino acid isolated from the plant wall glycoprotein extensin.[12] Since its structure is a key element for a large class of natural products bearing an endocyclic diaryl ether, (*S,S*)-isodityrosine has served as a test for a number of synthetic methods.[3−5,13] Obviously, the most straightforward and practical approach to it is from two natural

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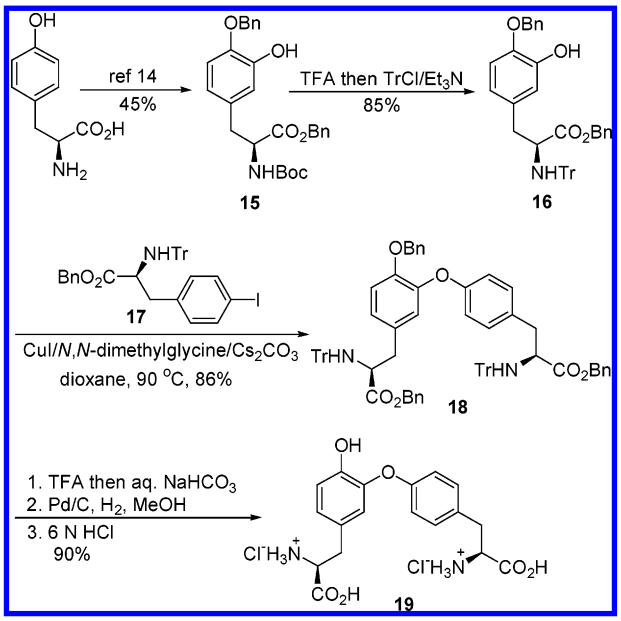
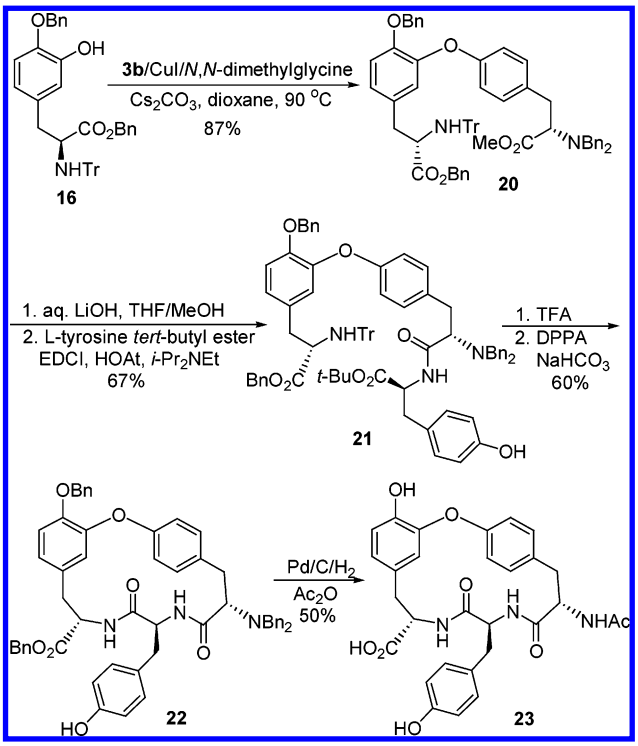
(13) For recent examples, see (a) Gupta, A. Sen, S.; Harmata, M.; Pulley, S. R. *J. Org. Chem.* **2005**, *70*, 7422. (b) Jung, M. E.; Lazarova, T. *J. Org. Chem.* **1999**, *64*, 2976. (c) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389. (d) Jørgensen, K. B.; Gautun, O. R. *Tetrahedron* **1999**, *55*, 10527.

SCHEME 2



SCHEME 3



aromatic amino acids. Up to this date, this ideal manner was achieved only by Jung and Lazarova,[13b] who completed the synthesis via coupling of an L-phenylalanine-derived arylboronic acid and an L-tyrosine derivative.

As depicted in Scheme 2, our synthesis for (*S*,*S*)-isodityrosine **19** started from carbamate **15**, an L-dopa derivative prepared from L-tyrosine in five steps and 45% overall yield.[14] Cleavage of the Boc group in **15** with TFA followed by reacting the resultant amine with trityl chloride produced *N*-trityl amino ester **16**. Coupling of this ester with an L-phenylalanine-derived aryl iodide **17** under the catalysis of CuI/*N*,*N*-dimethylglycine afforded diaryl ether **18** in 86% yield. After removal of the trityl group in **18** by exposure to TFA, Pd/C-catalyzed hydrogenolysis was conducted to cleave all benzyl-protecting groups. Upon treatment with 6 N HCl, (*S*,*S*)-isodityrosine was isolated as its hydrochloride salt. Its analytical data were all identical with those reported.[13] This protocol was similar to that reported by Jung and Lazarova[13b] but was more practical because conversion of aryl iodide to the corresponding arylboronic acid was omitted.

Our next target molecule was K-13, a 17-membered cyclic peptide isolated from *Micromonospora halophytica* ssp. *exilisia* K-13. It has been shown to be a potent, noncompetitive inhibitor of angiotensin I-converting enzyme (ACE) and a weak inhibitor of aminopeptidase B.[15] During the past decades, considerable effects have been directed to its total synthesis and several successful approaches have been established.[5,6,16] Our synthetic pathway to this molecule is outlined in Scheme 3. CuI/*N*,*N*-dimethylglycine-catalyzed coupling of the L-dopa derivative **16** with the iodide **3b** delivered protected isodityrosine **20** in 87% yield. Selective hydrolysis of the methyl ester in **20** gave rise to a liberated acid, which was connected with L-tyrosine *tert*-butyl ester to furnish peptide **21**. Next, treatment of **21** with TFA removed the trityl and *tert*-butyl groups, and the resultant amino acid was subjected to macrocyclization mediated with DPPA and $NaHCO_3$ in a diluted DMF solution to afford lactam **22**. Finally, hydrogenolysis of **22** accompanied by acylation in methanol containing acetic anhydride provided K-13 in 50% yield. This protocol took only seven steps from a known intermediate **15** and gave a 14% overall yield, representing one of the simplest routes for assembling K-13.

In summary, we have developed a method for elaboration of enantiopure isodityrosine derivatives via an intermolecular Ullmann-type coupling reaction between L-tyrosine derivatives and L-phenylalanine-derived aryl iodides. The key issue is using N-trityl- or N,N-dibenzyl-protected amino esters as substrates and *N*,*N*-dimethylglycine as a reaction promoter to avoid racemization and achieve good coupling yields. Its value has been illustrated by successful applications in the total synthesis of (*S*,*S*)-isodityrosine and K-13. Further applications to assemble other related molecules and their analogues are in progress and will be reported in due course.

Experimental Section

General Procedure for CuI/*N*,*N*-dimethylglycine-Catalyzed Coupling Reaction of Aryl Iodides and Phenols. A Schlenk tube was charged with aryl iodide (0.5 mmol), phenol (0.75 mmol), CuI (0.15 mmol), *N*,*N*-dimethylglycine hydrochloride salt (0.5 mmol), Cs_2CO_3 (1.5 mmol), and 2 mL of 1, 4-dioxane, evacuated, and backfilled with argon. The reaction mixture was stirred at 90 °C until the conversion was completed as detected by TLC. The suspension was filtered and the filtrate was concentrated, followed by column chromatography on silica gel (eluting with 1:100 to 1:5 ethyl acetate/petroleum ether) to provide the desired product.

(*S*)-3-[4-(4-Acetylphenoxy)phenyl]-2-*tert*-butoxycarbonylaminopropionic Acid Methyl Ester 8a. $[\alpha]_D^{25}$ +36.5 (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, J = 9.0 Hz, 2H), 7.17 (d, J = 9.0 Hz, 2H), 7.01 (d, J = 9.0 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 5.06 (d, J = 7.2 Hz, 1H), 4.64 (m, 1H), 3.74 (s, 3H), 3.18 (m, 2H), 2.58 (s, 3H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ

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196.3, 172.0, 161.6, 154.8, 154.2, 132.4, 131.6, 130.6, 130.3, 120.0, 117.0, 79.5, 54.3, 51.9, 37.4, 28.0, 21.1; ESI-MS *m/z* 436.2 (M + Na)$^+$; HRMS calcd for $C_{23}H_{27}NO_6Na$ (M + Na)$^+$ 436.1750, found 436.1731.

(*S*)-3-[4-(4-Acetylphenoxy)phenyl]-2-benzyloxycarbonylaminopropionic Acid Methyl Ester 8b. $[\alpha]_D^{25}$ +38.7 (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 9.0 Hz, 2H), 7.39 (m, 5H), 7.13 (d, J = 9.0 Hz, 2H), 6.97 (m, 4H), 5.27 (m, 1H), 5.11 (m, 2H), 4.65 (m, 1H), 3.74 (s, 3H), 3.18 (m, 2H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 196.7, 171.8, 161.7, 155.5, 154.5, 136.1, 132.0, 131.9, 130.8, 130.5, 128.5, 128.2, 128.1, 120.1, 117.3, 67.0, 54.7, 52.4, 37.5, 26.4; IR (film) 3414, 2970, 1749, 1712, 1675, 1596 cm^{-1}; ESI-MS *m/z* 470.1 (M + Na)$^+$; HRMS calcd for $C_{26}H_{25}NO_6Na$ (M + Na)$^+$ 470.1574, found 470.1573.

(*S*)-3-[4-(4-Acetylphenoxy)phenyl]-2-(tritylamino)propionic Acid Methyl Ester 8c. $[\alpha]_D^{25}$ +57.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, J = 8.4 Hz, 2H), 7.43 (m, 6H), 7.20 (m, 11H), 7.00 (m, 4H), 3.61 (m, 1H), 3.06 (s, 3H), 2.97 (m, 2H), 2.65 (d, J = 11.1 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 196.8, 174.8, 162.2, 154.3, 145.9, 134.0, 131.9, 131.5, 130.7, 128.9, 128.2, 127.9, 126.7, 126.5, 120.1, 117.2, 71.1, 58.3, 51.4, 41.7, 26.5; IR (film) 3317, 3057, 3021, 1738, 1681, 1594 cm^{-1}; ESI-MS *m/z* 578.3 (M + Na)$^+$; HRMS calcd for $C_{37}H_{33}NO_4Na$ (M + Na)$^+$ 578.2302, found 578.2301.

(*S*)-3-[4-(4-Acetylphenoxy)phenyl]-2-dibenzylaminopropionic Acid Methyl Ester 8d. $[\alpha]_D^{25}$ −37.6 (*c* 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, J = 8.7 Hz, 2H), 7.29 (m, 10H), 7.02 (m, 4H), 6.95 (d, J = 8.4 Hz, 2H), 3.98 (d, J = 14.1 Hz, 1H), 3.77 (s, 3H), 3.70 (t, J = 7.5 Hz, 1H) 3.57 (d, J = 14.1 Hz, 2H), 3.15 (dd, J = 14.1, 6.6 Hz, 1H), 3.00 (d, J = 14.1, 8.7 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 196.4, 172.4, 162.0, 153.8, 139.2, 134.8, 131.8, 131.5, 131.1, 130.7, 128.8, 126.9, 120.0, 116.7, 61.9, 54.2, 51.0, 34.9, 26.2; IR (film) 3030, 2951, 1732, 1681, 1595 cm^{-1}; ESI-MS *m/z* 494.2 (M + H)$^+$; HRMS calcd for $C_{32}H_{32}NO_4$ (M + H)$^+$ 494.2326, found 494.2329.

(*S*)-3-[4-(4-Acetylphenoxy)phenyl]-2-(benzylmethylamino)-propionic Acid Methyl Ester 8e. $[\alpha]_D^{25}$ −39.2 (*c* 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 9.0 Hz, 2H), 7.29 (m, 7H), 7.0 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 3.84 (d, J = 14.1 Hz, 1H), 3.72 (s, 3H), 3.62 (m, 1H), 3.60 (m, 1H), 3.15 (dd, J = 14.1, 7.8 Hz, 1H), 2.98 (d, J = 14.1, 6.3 Hz, 1H), 2.57 (s, 3H), 2.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 196.4, 171.9, 162.0, 153.5, 138.8, 134.7, 131.4, 130.6, 130.4, 128.4, 128.0, 126.9, 119.8, 116.7, 66.7, 58.7, 50.9, 37.5, 34.8, 26.2; IR (film) 1732, 1681, 1595 cm^{-1}; ESI-MS *m/z* 418.1 (M + H)$^+$; HRMS calcd for $C_{26}H_{28}NO_4$ (M + H)$^+$ 418.2013, found 418.2024.

(*S*)-3-[4-(4-Acetylphenoxy)phenyl]-2-benzylaminopropionic Acid Methyl Ester 8f. $[\alpha]_D^{25}$ +11.8 (*c* 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 9.0 Hz, 2H), 7.29 (m, 5H), 7.21 (d, J = 9.0 Hz, 2H), 6.97 (m, 4H), 3.87 (d, J = 12.9 Hz, 1H), 3.68 (s, 3H), 3.63 (m, 1H), 3.54 (t, J = 6.9 Hz, 1H), 2.96 (m, 2H), 2.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 196.6, 174.8, 162.0, 154.1, 139.5, 133.8, 131.8, 130.8, 130.5, 128.3, 128.1, 127.0, 120.0, 117.1, 61.9, 51.9, 51.6, 38.9, 26.3; IR (film) 3337, 1735, 1677, 1597 cm^{-1}; ESI-MS *m/z* 404.2 (M + H)$^+$; HRMS calcd for $C_{25}H_{26}NO_4$ (M + H)$^+$ 404.1856, found 404.1852.

(*S*)-3-[4-(4-Cyanophenoxy)phenyl]-2-(tritylamino)propionic Acid Methyl Ester 9. $[\alpha]_D^{25}$ +59.6 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, J = 8.7 Hz, 2H), 7.40 (m, 6H), 7.20 (m, 11H), 7.00 (m, 4H), 3.60 (m, 1H), 3.07 (s, 3H), 2.98 (d, J = 6.6 Hz, 2H), 2.64 (d, J = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.7, 161.8, 153.6, 145.9, 134.6, 134.2, 131.7, 128.8, 127.9, 126.5, 120.2, 118.9, 117.9, 105.8, 71.1, 58.2, 51.4, 41.6; IR (film) 3318, 3057, 1737, 1597 cm^{-1}; ESI-MS *m/z* 561.2 (M + Na)$^+$; HRMS calcd for $C_{36}H_{30}N_2O_3Na$ (M + Na)$^+$ 561.2149, found 561.2162.

(*S*)-3-[4-(4-Methoxyphenoxy)phenyl]-2-(tritylamino)propionic Acid Methyl Ester 10. $[\alpha]_D^{25}$ +59.1 (*c* 0.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41 (m, 6H), 7.20 (m, 11H), 6.99 (m, 2H), 6.90 (m, 4H), 3.80 (s, 3H), 3.54 (m, 1H), 3.05 (s, 3H), 2.92 (d, J = 6.0 Hz, 2H), 2.62 (d, J = 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.9, 157.4, 155.9, 150.4, 145.9, 131.6, 131.0, 128.9, 127.8, 126.4, 120.7, 117.5, 114.9, 71.1, 58.4, 55.7, 51.4, 41.6; IR (film) 3316, 3057, 3000, 1737, 1499 cm^{-1}; ESI-MS *m/z* 566.2 (M + Na)$^+$; HRMS calcd for $C_{36}H_{33}NO_4Na$ (M + Na)$^+$ 566.2301, found 566.2280.

(*S*)-2-Dibenzylamino-3-(4-*p*-tolyloxyphenyl)propionic Acid Methyl Ester 11. $[\alpha]_D^{25}$ −40.8 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (m, 12H), 6.85 (m, 6H), 5.20 (d, J = 12.0 Hz, 1H), 3.89 (d, J = 14.1 Hz, 2H), 3.65 (s, 3H), 3.57 (m, 1H), 3.48 (d, J = 14.1 Hz, 2H), 2.91 (m, 2H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 172.8, 155.9, 155.1, 139.2, 132.7, 132.5, 130.6, 130.1, 128.7, 128.1, 126.9, 118.6, 118.4, 62.2, 54.3, 51.2, 34.9, 20.7; ESI-MS *m/z* 466.2 (M + H)$^+$; HRMS calcd for $C_{31}H_{32}NO_3$ (M + H)$^+$ 466.2377, found 466.2370.

(*S*)-3-(4-{4-[(*S*)-2-Methoxycarbonyl-2-tritylamino]ethyl}phenoxy)phenyl)-2-(tritylamino)propionic Acid Methyl Ester 12. $[\alpha]_D^{25}$ +71.9 (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (m, 13H), 7.25 (m, 21H), 6.92 (d, J = 7.2 Hz, 2H), 3.58 (m, 2H), 3.05 (s, 6H), 2.93 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.8, 156.1, 145.8, 132.3, 131.0, 128.7, 127.7, 126.3, 118.5, 71.0, 58.3, 51.3, 41.5; IR (film) 3057, 3031, 1737, 1598 cm^{-1}; ESI-MS *m/z* 879.4 (M + Na)$^+$; HRMS calcd for $C_{58}H_{52}N_2O_5Na$ (M + Na)$^+$ 879.3768, found 879.3749.

(*S*)-3-{4-[4-((*S*)-2-Dibenzylamino-2-methoxycarbonylethyl)-phenoxy]phenyl}-2-(tritylamino)propionic Acid Methyl Ester 13. $[\alpha]_D^{25}$ +16.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 (m, 6H), 7.25 (m, 21H), 6.95 (m, 6H), 3.98 (m, 2H), 3.75 (s, 3H), 3.68 (s, 1H), 3.54 (m, 3H), 3.07 (s, 3H), 2.95 (m, 3H), 2.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.8, 172.8, 155.5, 145.8, 139.2, 133.1, 132.1, 131.0, 130.6, 128.8, 128.7, 128.3, 127.8, 127.0, 126.4, 118.7, 118.2, 71.0, 62.2, 58.3, 54.4, 51.3, 51.2, 41.5, 35.0; IR (film) 3059, 3029, 1733, 1601 cm^{-1}; ESI-MS *m/z* 795.3 (M + H)$^+$; HRMS calcd for $C_{53}H_{51}N_2O_5$ (M + H)$^+$ 795.3792, found 795.3782.

(*S*)-3-{4-[4-((*S*)-2-Benzyloxycarbonyl-2-dibenzylaminoethyl)-phenoxy]phenyl}-2-dibenzylaminopropionic Acid Methyl Ester 14. $[\alpha]_D^{25}$ −57.1 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 5H), 7.20 (m, 20H), 5.30 (m, 2H), 3.96 (m, 4H), 3.75 (s, 3H), 3.67 (m, 2H), 3.52 (m, 4H), 3.06 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 172.8, 172.1, 155.9, 155.8, 139.2, 139.1, 132.9, 132.8, 130.6, 128.7, 128.6, 128.5, 128.3, 128.2, 127.0, 126.9, 118.5, 118.4, 66.1, 62.3, 62.2, 54.4, 54.3, 51.2, 35.0, 34.9; IR (film) 3063, 3030, 1732, 1603, 1502 cm^{-1}; ESI-MS *m/z* 809.4 (M + H)$^+$; HRMS calcd for $C_{54}H_{53}N_2O_5$ (M + H)$^+$ 809.3949, found 809.3953.

(*S*)-3-(4-Benzyloxy-3-hydroxyphenyl)-2-(tritylamino)propionic Acid Benzyl Ester 16. A solution of **15** (6.0 g, 12.6 mmol) in 75 mL of CH_2Cl_2 and 25 mL of TFA was stirred for 4 h at room temperature before it was concentrated to dryness. The residue was dissolved in 30 mL of DMF. TrCl (4.2 g, 15.1 mmol) and Et_3N (5.3 mL, 37.8 mmol) were added at 0 °C. The mixture was stirred for 4 h before it was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography of the residue afforded 6.6 g (85%) of **16**: $[\alpha]_D^{25}$ +37.7 (*c* 0.63, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 11H), 7.15 (m, 12H), 6.93 (m, 2H), 6.52 (m, 2H), 6.49 (m, 1H), 5.52 (s, 1H), 4.97 (s, 2H), 4.44 (d, J = 12.6 Hz, 1H), 4.19 (d, J = 12.6 Hz, 1H), 3.52 (m, 1H), 2.90 (dd, J = 13.5, 6.3 Hz, 1H), 2.76 (dd, J = 13.5, 7.5 Hz, 1H), 2.60 (d, J = 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.4, 145.8, 145.5, 144.6, 136.3, 135.2, 130.8, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.7, 127.6, 126.3, 121.1, 116.1, 111.8, 71.0, 66.3, 58.3, 41.7; IR (film) 3528, 3059, 1732, 1594, 1508 cm^{-1}; ESI-MS *m/z* 642.3 (M + Na)$^+$; HRMS calcd for $C_{42}H_{37}NO_4Na$ (M + Na)$^+$ 642.2615, found 642.2603.

(*S*)-3-(4-Benzyloxy-3-{4-[(*S*)-2-benzyloxycarbonyl-2-(tritylamino)ethyl]phenoxy}phenyl)-2-(tritylamino)propionic Acid Ben-

zyl Ester 18. A mixture of **16** (310 mg, 0.5 mmol), **17** (467 mg, 0.75 mmol), CuI (28.5 mg, 0.15 mmol), *N*,*N*-dimethylglycine hydrochloride (70 mg, 0.5 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol) in 2 mL of 1,4-dioxane was stirred for 30 h at 90 °C. The mixture was filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo and the residue was chromatographed to afford 479 mg (86%) of **18**: $[\alpha]_D^{25}$ +40.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43 (m, 14H), 7.22 (m, 29H), 6.99 (m, 5H), 6.88 (m, 2H), 6.78 (m, 2H), 5.05 (s, 2H), 4.52 (m, 2H), 4.44 (m, 2H), 4.27 (m, 2H), 3.57 (m, 2H), 2.92 (m, 4H), 2.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.4, 174.2, 157.2, 149.5, 145.9, 145.8, 145.1, 137.0, 135.3, 131.0, 130.9, 130.8, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.0, 125.3, 125.0, 123.5, 121.2, 116.6, 116.2, 115.1, 71.1, 71.0, 70.9, 66.4, 66.3, 58.3, 58.2, 41.5, 41.3; IR (film) 3059, 1734, 1596, 1506 cm^{-1}; ESI-MS *m*/*z* 1137.4 (M + Na)$^+$; HRMS calcd for $C_{77}H_{66}N_2O_6$Na (M + Na)$^+$ 1137.4813, found 1137.4811.

(*S*,*S*)-Isodityrosine 19. A solution of **18** (111 mg, 0.1 mmol) in 2 mL of CH_2Cl_2/TFA (1:1) was stirred for 2 h at room temperature and then concentrated in vacuo. The reaction was quenched by adding aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography of the residue afforded the crude amine.

The above amine was dissolved in 1 mL of MeOH, and then Pd/C (30 mg) was carefully added to the solution. After being stirred for 24 h under H_2 atmosphere, the mixture was filtered through Celite. The filtrate was concentrated to dryness in vacuo. The residue was added with 6 N HCl (2 mL) and stirred for 5 h at 60 °C. The mixture was extracted with EtOAc. The aqueous phase was concentrated in vacuo to afford the hydrochloride salt of **19** (39 mg, 90%): $[\alpha]_D^{25}$ −24.2 (*c* 0.2, MeOH); ^{1}H NMR (D_2O, 300 MHz) δ 7.18 (d, *J* = 8.4 Hz, 2H), 7.00 (br s, 2H), 6.89 (m, 3H), 4.14 (m, 2H), 3.10 (m, 4H); IR (film) 3413, 3100, 1740, 1639, 1508 cm^{-1}; ESI-MS *m*/*z* 361.1 (M + H)$^+$; HRMS calcd for $C_{18}H_{21}N_2O_6$ (M + H)$^+$ 361.1395, found 361.1402.

(*S*)-3-{4-Benzyloxy-3-[4-(S)-2-dibenzylamino-2-methoxycarbonylethyl]phenoxy}phenyl}-2-(tritylamino)propionic Acid Benzyl Ester 20. A mixture of **16** (310 mg, 0.5 mmol), **3b** (364 mg, 0.75 mmol), CuI (28.5 mg, 0.15 mmol), *N*,*N*-dimethylglycine hydrochloride (70 mg, 0.5 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol) in 2 mL of 1,4-dioxane was stirred for 30 h at 90 °C. The mixture was filtered through Celite and washed with EtOAc. The filtrate was concentrated in vacuo, and the residue was chromatographed to afford 425 mg (87%) of **20**: $[\alpha]_D^{25}$ −9.0 (*c* 0.78, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 10H), 7.23 (m, 24H), 7.00 (m, 2H), 6.97 (m, 6H), 5.08 (s, 2H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 1H), 3.97 (d, *J* = 14.1 Hz, 2H), 3.67 (s, 3H), 3.66 (m, 1H), 3.55 (m, 3H), 3.10 (m, 1H), 2.92 (m, 1H), 2.82 (m, 2H), 2.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.1, 172.7, 156.6, 149.2, 145.8, 145.3, 139.2, 136.9, 135.2, 131.9, 130.9, 130.3, 128.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.0, 126.9, 126.3, 125.8, 123.0, 116.8, 114.9, 71.0, 70.9, 66.3, 62.4, 58.1, 51.1, 41.3, 35.0; ESI-MS *m*/*z* 977.4 (M + H)$^+$; HRMS calcd for $C_{66}H_{61}N_2O_6$ (M + H)$^+$ 977.4524, found 977.4522.

(*S*)-3-[4-Benzyloxy-3-(4-{(*S*)-2-[(*S*)-1-*tert*-butoxycarbonyl-2-(4-hydroxy-phenyl)ethylcarbamoyl]-2-dibenzylaminoethyl}-phenoxy)phenyl]-2-(tritylamino)-propionic Acid Benzyl Ester 21. A mixture of **20** (500 mg, 0.51 mmol), LiOH (64 mg, 1.5 mmol), THF (3 mL), MeOH (1 mL), and H_2O (1 mL) was stirred at 0 °C for 30 min. After the solution was treated with 1 N HCl to adjust the pH to about 2, it was extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to give crude acid (374 mg, 76%), which was dissolved in DMF (9 mL). To this solution were added sequentially l-tyrosine *tert*-butyl ester (138 mg, 0.58 mmol), HOAt (105 mg, 0.77 mmol), EDCI (148 mg, 0.77 mmol), and DIPEA (0.27 mL, 1.54 mmol) at 0 °C. The mixture was stirred for 3 h at 0 °C and 11 h at room temperature before it was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography of the residue afforded 404 mg (88%) of **21**: $[\alpha]_D^{25}$ +1.7 (*c* 0.62, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (m, 7H), 7.25 (m, 30H), 6.93 (m, 7H), 6.58 (d, *J* = 8.1 Hz, 2H), 5.05 (s, 2H), 4.65 (m, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 3.52 (m, 6H), 3.28 (m, 1H), 2.80 (m, 6H), 2.60 (m, 1H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 174.3, 172.2, 170.7, 156.6, 155.0, 149.2, 145.8, 145.3, 138.6, 136.9, 135.2, 133.9, 130.9, 130.4, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.1, 127.0, 126.3, 125.8, 123.1, 117.0, 115.3, 115.0, 82.2, 71.0, 70.9, 66.4, 63.6, 58.2, 54.4, 54.2, 41.3, 37.7, 31.2, 27.9; ESI-MS *m*/*z* 1182.4 (M + H)$^+$; HRMS calcd for $C_{78}H_{75}N_3O_8$Na (M + Na)$^+$ 1204.5446, found 1204.5434.

(9*S*,12*S*,15*S*)-4-Benzyloxy-15-dibenzylamino-12-(4-hydroxy-benzyl)-11,14-dioxo-2-oxa-10,13-diazatricyclo[15.2.2.1^{3,7}]docosa-1(20),3(22),4,6,17(21),18-hexaene-9-carboxylic Acid Benzyl Ester 22. A solution of **21** (185 mg, 0.16 mmol) in 2 mL of CH_2Cl_2/TFA (1:1) was stirred for 2 h at room temperature and then concentrated in vacuo. The residue was dissolved in DMF (32 mL) before $NaHCO_3$ (80 mg, 0.95 mmol) and DPPA (86.7 mg, 0.32 mmol) were added. After it was stirred for 3 days at 0 °C, the solution was diluted with 50 mL of EtOAc and water (1:1). The water phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography afforded **22** (81 mg, 60%): $[\alpha]_D^{25}$ −72.0 (*c* 0.55, $CHCl_3$); ^{1}H NMR ($CHCl_3$, 300 MHz) δ 7.44 (m, 22H), 7.15 (d, *J* = 8.7 Hz, 1H), 7.04 (m, 3H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.15 (dd, *J* = 8.7, 1.5 Hz, 1H), 5.96 (d, *J* = 1.8 Hz, 1H), 5.77 (d, *J* = 6.3 Hz, 1H), 5.54 (d, *J* = 5.1 Hz, 1H), 5.10 (m, 4H), 4.35 (m, 1H), 4.17 (d, *J* = 14.1 Hz, 2H), 3.99 (m, 1H), 3.68 (d, *J* = 14.1 Hz, 2H), 2.86 (m, 4H), 2.72 (m, 3H); ^{13}C NMR ($CHCl_3$, 300 MHz) 171.0, 170.4, 170.0, 155.2, 154.9, 149.6, 147.5, 139.8, 137.1, 134.8, 133.7, 131.7, 130.4, 129.7, 128.8, 128.7, 128.5, 128.4, 128.3, 127.9, 127.8, 127.2, 127.1, 122.8, 122.3, 121.1, 118.1, 115.5, 115.1, 114.1; IR (film) 3392, 2962, 2926, 1742, 1650, 1508, 1454, 1263, 1216, 1127, 697 cm^{-1}; ESI-MS *m*/*z* 886.4 (M + H)$^+$; HRMS calcd for $C_{55}H_{52}N_3O_7$ (M + H)$^+$ 866.3800, found 866.3794.

K-13 (23). To a solution of **22** (20 mg, 0.023 mmol) in 1 mL methanol were added Pd/C (10 mg) and Ac_2O (2.1 μL). The mixture was stirred under 50 psi of H_2 atmosphere for 2 days and then filtered and evaporated in vacuo. Flash chromatography afforded **23** (6 mg, 50%): $[\alpha]_D^{25}$ −6.4 (*c* 0.48, MeOH); ^{1}H NMR (MeOH-d_4, 300 MHz) δ 7.29 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.05 (dd, *J* = 8.1, 2.7 Hz, 1H), 6.97 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.68 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.64 (dd, *J* = 8.4, 3.0 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 2H), 6.33 (d, *J* = 1.5 Hz, 1H); 4.44 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.33 (dd, *J* = 12.0, 5.1 Hz, 1H), 4.10 (t, *J* = 6.0 Hz, 1H), 3.10 (dd, *J* = 15.0, 3.0 Hz), 3.05 (m, 1H), 2.96 (m, 4H), 2.01 (s, 3H); ^{13}C NMR (MeOH-d_4, 300 MHz) 173.2, 172.6, 172.2, 158.5, 157.5, 148.3, 133.2, 132.4, 132.3, 131.6, 130.4, 128.5, 125.6, 122.3, 121.1, 119.0, 117.9, 116.2, 57.6, 56.1, 53.8, 39.5, 39.0, 36.6, 22.7; IR (film) 3400 (br), 1740, 1670, 1590, 1516 cm^{-1}; ESI-MS *m*/*z* 548.3 (M + H)$^+$; HRMS calcd for $C_{29}H_{30}N_3O_8$ (M + H)$^+$ 548.2033, found 548.2027.

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