DOI: 10.1002/ejoc.201101057

Orthogonal Protecting Groups in the Synthesis of Tryptophanyl-Hexahydropyrroloindoles

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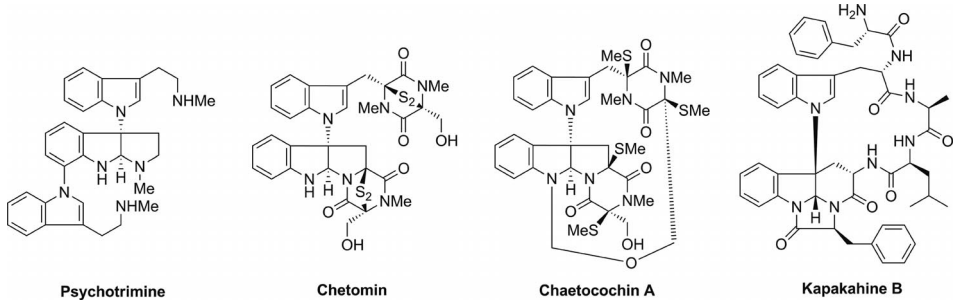
Keywords: Natural products / Heterocycles / Amino acids / Protecting groups

The synthesis of various polycyclic systems containing a C^{3a}–N^{i} bond between a hexahydropyrrolo[2,3-*b*]indole and an indole tryptophan is described here. A series of experiments were performed to determine the best combination of five orthogonal protecting groups and the best reaction conditions for formation of said bond, which is a common feature among many recently discovered marine natural products.

Introduction

The tricyclic motif hexahydropyrrolo[2,3-*b*]indole (HPI) is present in many natural compounds with important bioactivities.[1] These compounds all feature a substituent at the 3a-position of the HPI such as a methyl group, in (–)-physostigmine;[2] a prenyl, in flustramines,[3] brevicompanines,[4] and roquefortines;[5] and a newly discovered HPI linked by one aromatic carbon, in idiospermuline,[6] psychotridine,[7] and quadrigemine.[8] Recently isolated natural compounds such as psychotrimine,[9] chaetomin, and the chaetocochins[10] contain an unusual bond between the 3a-position of the HPI and the indole nitrogen of either a tryptamine or a tryptophan (Scheme 1). Kapakahines are natural products with a bond between the C^{4a} of an α-carboline and the indole nitrogen of an N-Trp.[11]

To date, four total syntheses of psychotrimine have been reported.[12] Takayama and co-workers were the first to synthesize this compound,[12a] assembling the HPI motif from a phenylacetonitrile that contained an indoline at the appropriate α-nitrile position. In contrast, Newhouse and Baran[12b] prepared psychotrimine through simultaneous formation of the HPI and the N–C^{3a} bond. They later employed the same strategy to synthesize kapakahines B and F,[13] and (+)-psychotetramine.[14]



Scheme 1. Natural products containing a bond between the C^{3a} of an HPI, or the C^{4a} of an α-carboline, and the indole nitrogen of either a tryptamine or a tryptophan.

During the course of the present work, Espejo and Rainier published a study on N–C^{3a} bond formation through bromo-displacement of 3a-bromo-HPIC with the N-anion of indole.[15] The same group harnessed this chemistry to obtain kapakahines E and F,[16] and, more recently, proposed a mechanism for the substitution.[17]

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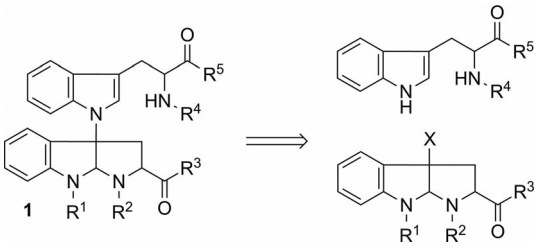
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101057.

Compound **1**, which contains a bond between the C^{3a} of HPI and the nitrogen atom of an indole, could be used as a scaffold for the synthesis of many natural products and analogues. In the work reported here, **1** was synthesized through nucleophilic substitution of the bromine at position 3a of 3a-bromo-HPI with an N-indole anion (Scheme 2). To ensure chemoselectivity during this chemistry, five orthogonal protecting groups were required. Studies to determine the best protecting groups and conditions for this bond formation were then performed and are described herein.



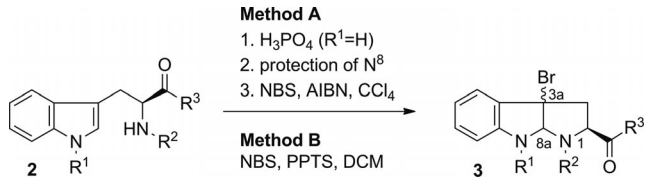
Scheme 2. Retrosynthesis of compound **1**.

Results and Discussion

First, various bromo analogues of 3a-bromo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole-2-carboxylate (3a-Br-HPI; **3**) were synthesized using two different procedures, which were subsequently compared for performance (Table 1). The first approach followed the route described by Taniguchi and Hino,[18] and was based on cyclization of a protected Trp in acidic medium, followed by aniline protection and subsequent benzylic bromination of HPI-2-carboxylate. The second procedure involved a one-step bromination–cyclization of a completely protected Trp using *N*-bromosuccinimide (NBS) and pyridinium *p*-toluenesulfonate (PPTS).[19] The resulting products **3** and their stereochemistries (*endo*/*exo*) are listed in Table 1. For protection of the carboxylate moiety, common esters such as methyl, *tert*-butyl, and allyl were tested. On the other hand, for the amino function, both alkoxycarbonyl [i.e., *tert*-butoxycarbonyl (Boc), allyloxycarbonyl (Alloc), benzyloxycarbonyl (Cbz), 2,2,2-trichloroethoxycarbonyl (Troc), and methoxycarbonyl (Moc)], and sulfonyl [i.e., 2-nitrobenzenesulfonyl (Nosyl) and SO_2Ph] were tested. Although a three-way orthogonal system is desirable (two amino and one carboxylic protecting groups), the use of the same amino protecting groups ($R^1 = R^2$) for both amino groups was also studied (Table 1, entries 2, 3, and 16) bearing in mind the different nucleophilicity of the amino functions in forthcoming experiments. Additionally, protected amino acids (R^2 and R^3 Table 1, entries 14–16) were assayed with the aim of studying the effects of size and/or electronic properties of the protecting groups.

The overall transformation of L-Trp-OMe (the starting material) into **3** was highly demanding, as illustrated by the yields, which ranged from poor to moderate. Method B, which is shorter, gave better yields for the same set of protecting groups (Table 1, entries 7, 12, and 13) and had the important additional advantage of being amenable to the use of various protecting groups for the α-amino group (R^2). Cyclization with H_3PO_4 (Method A) gave better yields when methoxycarbonyl (R^2 = Moc) was used as the N^{α}-Trp protecting group compared to those obtained when trichloroethoxycarbonyl (R^2 = Troc) was used (see Table 1, entries 12 and 7, respectively).

Table 1. Synthesis of the bromo-compounds **3a**–**p**.



Entry	Comp.	R^1	R^2	R^3	Method (yield%)	*endo*/*exo*
1	**3a**	Boc	Alloc	OMe	B (83)	*exo*
2	**3b**	Boc	Boc	OAllyl	B (30)[a]	*exo*
3	**3c**	Boc	Boc	OMe	B (86)	4:96[b]
4	**3d**	Boc	Cbz	OMe	B (78)	*exo*
5	**3e**	Boc	Troc	OMe	B (77)	11:89[c]
6	**3f**	Nosyl	Cbz	O*t*Bu	B (80)	7:93[c]
7	**3g**	Nosyl	Troc	OMe	A (9)	*endo*
					B (57)	8:92[c]
8	**3h**	Nosyl	Troc	O*t*Bu	B (59)	6:94[b]
9	**3i**	SO_2Ph	Boc	OMe	B (92)	7:93[b]
10	**3j**	SO_2Ph	Cbz	OMe	B (82)	4:96[b]
11	**3k**	SO_2Ph	Cbz	O*t*Bu	B (83)	*exo*
12	**3l**	SO_2Ph	Moc	OMe	A (37)	*endo*
					B (96)	5:95[b]
13	**3m**	SO_2Ph	Moc	O*t*Bu	A (28)	91:9[c]
					B (58)	25:75[c]
14	**3n**	Boc	N^{α}-Alloc-Ala	OMe	B (47)	*exo*
15	**3o**	Boc	Alloc	Ile-OMOM	B (47)[a]	*exo*
16	**3p**	Boc	Boc	Ile-OAllyl	B (41)[a]	*exo*

[a] Compounds **3b**, **3o**, and **3p** were synthesized from **3c**, **3a**, and **3c**, respectively, after hydrolysis and subsequent esterification or coupling with the protected Ile (see the Supporting Information). [b] Ratio determined by HPLC analysis.[20] [c] Ratio determined by ^{1}H NMR spectroscopic analysis.

Despite numerous attempts under diverse conditions, we were unable to remove the Moc group from the N^1 of HPI-2-carboxylate.[21] Furthermore, to the best of our knowledge,[1] there have been no reports of removal of the Moc group from N^8 of HPI-2-carboxylate; instead, this group is typically reduced to obtain a *N*-Me product.[12b,22]

Compounds **3b** and **3c** possess two Boc groups at positions N^1 and N^8 that could be cleaved simultaneously; however, the amine of N^1 is more reactive than the aniline of N^8, which enabled chemoselective acylation of N^1, as reported by Kamenecka and Danishefsky.[23]

The ^{1}H NMR signals corresponding to the protecting groups of R^2 – namely, the signals for the CH_2 of Cbz or Troc – are broad or split, because the protons are diastereotopic.

The difference in stereochemistry of the products **3** obtained from each method is noteworthy. Comparison of the ^{1}H NMR spectra of the products **3g** obtained from Method

A and from Method B revealed significant differences in the signals for the proton at position 2 (δ = 4.67 vs. 3.98 ppm, respectively) and for the methyl ester (δ = 3.21 vs. 3.74 ppm, respectively). Based on these data, the stereochemistry of the product from Method A was determined to be *endo*-**3g**, and that of the product from Method B, *exo*-**3g** (see Figure 1). The diamagnetic anisotropy of the phenyl ring shields the *endo*-methyl group (δ = 3.21 ppm) and the *exo*-H2 (δ = 3.98 ppm).[24] The same phenomenon occurred with the *endo*/*exo* products **3l** and **3m** obtained with the appropriate method (see the Supporting Information).

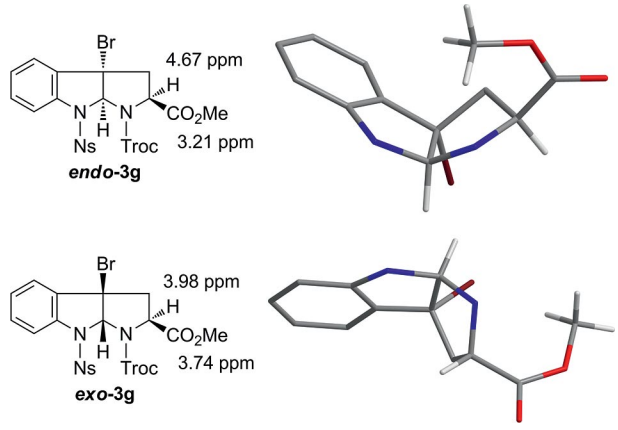


Figure 1. Comparison of the ^{1}H NMR spectroscopic data for *endo* and *exo* **3g** (left). Three-dimensional models of the corresponding tricyclic systems with *N*-protecting groups omitted for clarity (right).[25]

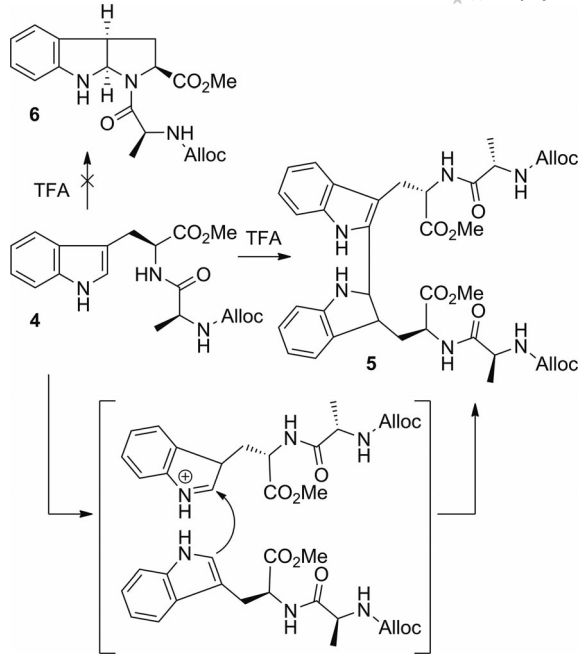
Compounds **3a**, **3b**, **3d**, **3k**, and **3n**–**p** (Table 1, entries 1, 2, 4, 11, and 14–16) revealed the presence of only one diastereomer in the NMR spectroscopic data. Their stereochemical assignments were determined by comparing the chemical shifts of the proton and the substituent at C^2 of HPI.

To obtain a more versatile intermediate during the synthesis of **3n**, **3o**, and **3p** by Method B, protected Ala or Ile were used as N^{α}- (R^2 in compound **2**, Table 1) and *O*- (R^3 in compound **2**, Table 1) protecting groups, respectively.

However, in the synthesis of compound **6**, bromination at position 3a (Method A) required an indirect route because subjecting dipeptide **4**, which was N^{α}-Alloc-Ala-protected, to the acidic conditions for cyclization furnished the dimer **5** (Scheme 3). Formation of **5** could be explained by electrophilic substitution between **4** and the indoline, which forms upon protonation.

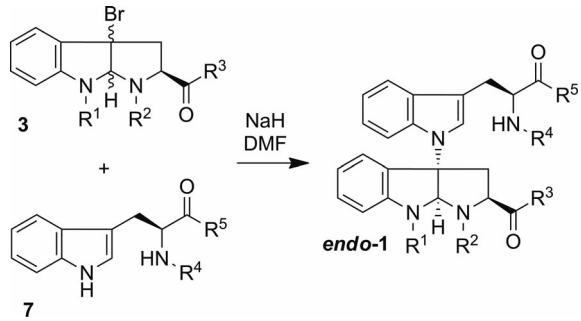
Consequently, in the first step of HPI formation using Method A, use of an N^{α}-carbamate protecting group, instead an amide, is rather important.

The second part of this work comprised formation of the bond between the C^{3a} of HPI and the N^{i} of Trp. Several pairs of base and solvent were tested to generate the indole anion that would drive the substitution to give compound **1**.[26] The best conditions involved the use of NaH in *N*,*N*-dimethylformamide (DMF) at 70 °C for 1.5 h. Each bromoderivative (**3a**–**p**) was tested with several protected Trp compounds. A significant signal in the ^{13}C NMR spectroscopic data for compounds **1** and **3** was the chemical shift of the quaternary C^{3a}, which is less shielded in **1** (δ = 72.4 to 82.2 ppm) than in **3** (δ = 53.7 to 67.9 ppm). The results of these substitutions are summarized in Table 2.



Scheme 3. Dimerization of **4** under acidic conditions.

Table 2. Nucleophilic substitution of 3a-Br-HPI.



Entry	3[a]	R^4	R^5	3[b]	7[b]	1[b]	Comp. [%][c]
1	*exo*-**3a**	Phth	OMe	39	18	43	**1a** (41)
2	*exo*-**3c**	Moc	OMe	49	22	29	**1b** (20)
3	*exo*-**3c**	Phth	OMe	66	11	24	**1c** (21)
4	*exo*-**3d**	Phth	OMe	28	14	58	**1d** (26)
5	*endo*-**3g**	Alloc	OMe	24	21	48	**1e** (29)
6	*exo*-**3g**	Alloc	O*t*Bu	62	22	15	**1f** (22)
7	*endo*-**3l**	Alloc-Ile	O*t*Bu	–	24	50	**1g** (41)
8	*endo*-**3l**	Moc	OMe	–	1	91	**1h** (77)
9	*endo*-**3m**	Boc-Ile	OAllyl	29	20	48	**1i** (30)
10	*exo*-**3p**	Phth	OMe	13	42	11	**1j** (30)

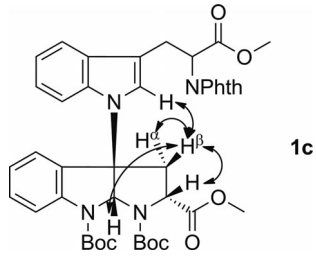
[a] See Table 1 for the protecting groups used in each compound **3**. [b] Percentage of each compound in the crude reaction product (determined by HPLC analysis).[20] [c] Yield of isolated compound.

The best yields of **1** in the nucleophilic substitution were found using **3a**, **3l**, **3m**, and **3p** (Table 2, entries 1 and 7–10, respectively). Moderate yields were obtained for the substi-

tutions with bromides **3c**, **3d**, and **3g** (Table 2, entries 3–6). However, very poor yields (less than 10%, data not shown) were observed when bromides **3b**, **3e**, **3f**, **3h**–**k**, and **3n** were treated with different protected versions of **7**, which contains two additional protecting groups.

The phthalamide (Phth) group was introduced as R^4 because it is orthogonal to the remaining protecting groups (Table 2, entries 1, 3, 4 and 10) and it eliminates all the N^{α} acid protons in **7**. The wide range of yields in the resulting substitution (from 21 to 41%) demonstrates the importance of the protecting groups in the starting bromide. Bromides **3l** and **3m** contain the same protecting groups in both amino groups of HPI (R^1 = SO_2Ph, R^2 = Moc). Interestingly, the yield was lower when the group at R^5 was *tert*-butyl ester (**1g**; Table 2, entry 7) compared to methyl ester (**1h**; Table 2, entry 8). Likewise, the yield was lower when R^3 was *tert*-butyl ester (**1i**; Table 2, entry 9) compared to methyl ester (**1h**; Table 2, entry 8). The same trend was observed for **1f** (Table 2, entry 6) and **1e** (Table 2, entry 5), albeit to a lesser extent; the *tert*-butyl in **1f** is more sterically hindered than the methyl ester in **1e**. The results obtained with a protected Ile-Trp dipeptide as nucleophile (Table 2, entries 7 and 9), and with a Br-HPI and a protected Ile (Table 2, entry 10), are interesting because they can serve as a stepping stone to the synthesis of peptides found in many natural compounds. Additionally, owing to this Ile protection, **1j** (R^3 = Ile-OAllyl; Table 2, entry 10) was obtained in higher yield than was **1c** (R^3 = OMe; Table 2, entry 3), the protecting groups of which were the same, except for R^3.

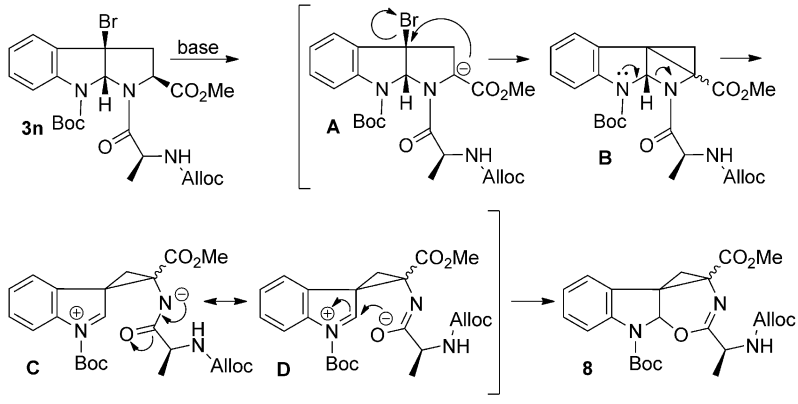
An interesting result of these experiments relates to the stereochemistry of compounds **1a**–**j**. All the substitutions furnished the more stable product *endo*-**1**, which shows a *cis* relative stereochemistry between protons H^2 and H^{8a} and the substituent at C^{3a} of HPI. ^{1}H NMR experiments show a chemical shift range of the methyl ester at C^2 [δ = 3.16–3.27 ppm] that is characteristic of *endo*-HPI.[24b] In addition, exhaustive 1D and 2D NMR experiments demonstrated the formation of *endo*-**1c** starting from a 4:96 *endo*/*exo* mixture of **3c**. Several gHSQC, HMBC, and NOESY experiments permitted the total stereochemistry assignment of **1c** (see the Supporting Information). The most significant result was obtained when irradiation at δ = 3.38 ppm ($H^{3\beta}$ of HPI) gave a positive NOE correlation with the protons at δ = 2.77 ($H^{3\alpha}$ of HPI), 4.83 (H^2 of HPI), 6.68 (H^{8a}), and 7.12 ppm (H^2 of Trp) (see Scheme 4). These results demonstrate that an identical substitution mechanism takes place for both *endo*-**3** and *exo*-**3**, and that epimerization of *exo*-**3** at C^2 of HPI occurs under the basic reaction conditions to give the more stable *endo*-products **1**.



Scheme 4. Significant NOE interactions used to assign the stereochemistry of the HPI motif in **1c**.

Reaction of bromide **3n** and N^{α}-Phth-Trp-OMe unexpectedly gave compound **8**. The product was characterized by 1D and 2D NMR analyses and by HRMS (see the Supporting Information). Important features of compound **8** are the lack of Br, the α-proton of the Trp, and the fact that the two protons of the cyclopropane CH_2 (δ = 3.43 and 3.91 ppm; 2 d, J = 15.4 Hz) only exhibit a geminal coupling constant. The significant difference in the chemical shift of the α-proton of the Ala in **3n** (δ = 5.02 ppm) and that of the Ala in **8** (δ = 4.11 ppm) could be justified by the different electronic effects in each compound. One hypothetical mechanism for the formation of **8** begins with deprotonation of the C^2 of the HPI, made possible by the basic conditions, followed by intramolecular bromine displacement and subsequent formation of cyclopropane, to afford intermediate **B** (Scheme 5). The high strain in **B** could drive opening of the aminal and subsequent cyclization, to give a more relaxed cyclohexane (Scheme 5).

Compound **3n** is a unique example of a Br-HPI with an amide as the protecting group of N^1, and **8** was isolated after the nucleophilic substitution reaction under the afore-



Scheme 5. Hypothetical mechanism for the formation of **8**.

mentioned conditions. Recently, Rainier and co-workers reported the behavior of **3c** under basic conditions (KO*t*Bu) and isolated a tetracycle-containing compound that resembles **B**.[27]

Conclusions

Various analogues of **3**, protected with different combinations of three orthogonal protecting groups, were prepared by two different routes. The routes were then compared for performance. Method A, which was based on sequential cyclization, protection, and bromination, provided the thermodynamic product, the *endo*-bromide; whereas Method B, which was based on a one-pot bromination/cyclization of a fully protected Trp, afforded mainly the kinetic product, the *exo*-bromide. The influence of the protecting groups on the formation of the N–C^{3a} bond between the Trp and HPI to give compounds **1f**, **1g**, and **1i** (containing five orthogonal protecting groups) and compounds **1a**, **1d**, **1e**, and **1j** (containing four orthogonal protecting groups) was also evaluated. Some of these compounds contain a protected Ile as R^4 to protect the α-amino Trp; the orthogonal protecting groups enable synthetic versatility for constructing more structurally complex molecules. The protecting groups in the bromides **3** determined the yields of compounds **1a**, **1c**, **1d**, and **1j**, the starting point of which (N^{α}-Phth-Trp-OMe; **7**) is the same. Moreover, the importance of the carbamate protecting group at R^2 should be emphasized; unexpectedly, compound **5** was obtained from an attempted cyclization of **4** in acidic medium (using an Ala amide bond for protecting the nitrogen atom in **4**) and compound **8** was obtained from an attempted nucleophilic substitution of the bromine atom at C^{3a} of **3n**.

Experimental Section

General Procedure for the Synthesis of 1: A solution of **6** (3.0 mmol) in dry DMF (10 mL) was added to a suspension of 60% NaH in mineral oil (1.2 equiv.) in dry DMF (20 mL), and the resulting mixture was stirred at room temperature for 15 min. A solution of **3** (3.0 mmol) in dry DMF (10 mL) was then added. The mixture was stirred at 70 °C for 1.5 h. The reaction mixture was then cooled to room temperature and quenched with H_2O. The aqueous phase was saturated with NaCl and extracted with EtOAc. The organic solution was dried with anhyd. Na_2SO_4, the solvent was removed, and the residue was purified by column chromatography on silica gel to afford **1**.

Compound 1a: Purified by flash chromatography (hexane/EtOAc, from 90:10 to 50:50); *endo*/*exo* (57:43) mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 and 1.49 (2× s, 9 H), 2.82 and 2.92 (2× d, J = 13.0 Hz, 1 H), 3.17 and 3.21 (2× s, 3 H), 3.33–3.45 (m, 1 H), 3.49–3.68 (m, 2 H), 3.76 (s, 3 H), 4.59–4.74 (m, 2 H), 4.88 (t, J = 9.8 Hz, 1 H), 5.08–5.16 (m, 1 H), 5.17–5.31 (m, 2 H), 5.85–5.99 (m, 1 H), 6.62–6.88 (m, 3 H), 6.95–7.14 (m, 4 H), 7.30 (dd, J = 7.4, 14.8 Hz, 1 H), 7.57 (t, J = 6.8 Hz, 1 H), 7.68 (dd, J = 3.1, 5.5 Hz, 1 H), 7.71 (dd, J = 3.0, 5.6 Hz, 1 H), 7.73–7.79 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4 (t), 28.1 (3× q), 38.1 (t), 52.2 (q), 52.3 (d), 52.5 and 52.8 (q), 53.4 (s), 59.3 and 59.4 (d), 66.6 (t), 79.6 (d), 82.2 (2× s), 110.6 (s), 111.2 and 111.3 (d), 117.6 and 117.7 (t), 119.2 and 119.3 (d), 120.0 (d), 122.3 and 122.4 (d), 123.4 (4× d), 124.4 and 124.7 (d), 129.7 (s), 129.8 (s), 130.9 (d), 131.6 (s), 131.7 (s), 132.5 (d), 134.0 (3× d), 134.7 (s), 143.3 (s), 143.4 (s), 151.8 (s), 151.9 (s), 167.2 (s), 167.4 (s), 169.4 (s), 170.6 (s) ppm. IR (KBr): $\tilde{\nu}$ = 2952, 1716, 1390, 1255, 1158, 1019, 721 cm^{-1}. HRMS (ESI): calcd for $C_{41}H_{40}N_4O_{10}Na$ [M + Na^+] 771.2642; found 771.2634.

Compound 1b: Purified by flash chromatography (hexane/EtOAc, from 80:20 to 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 9 h), 1.52 (s, 9 H), 2.98–3.20 (m, 3 H), 3.23 (s, 3 H), 3.54–3.65 (m, 7 H), 4.60 (m, 1 H), 4.90 (br. s, 1 H), 5.19 (t, J = 8.3 Hz, 1 H), 6.69 (d, J = 7.3 Hz, 1 H), 6.75 (s, 1 H), 7.07–7.33 (m, 5 H), 7.35–7.42 (m, 1 H), 7.52 (t, J = 7.5 Hz, 1 H), 7.67 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6 (t), 28.2 (3× q), 28.3 (3× q), 38.4 (t), 52.2 (q), 52.3 (q), 52.4 (q), 54.5 (d), 59.4 (d), 72.5 (s), 79.8 (d), 81.6 (s), 82.4 (s), 109.3 (s), 111.6 (d), 119.4 (d), 120.2 (2× d), 122.5 (d), 123.6 (d), 124.9 (d), 125.3 (d), 130.2 (s), 131.0 (d), 131.1 (s), 134.8 (s), 143.5 (s), 152.2 (s), 156.6 (s), 164.3 (s), 171.5 (s), 172.3 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3352, 2978, 1719, 1394, 1368, 1158, 740 cm^{-1}. HRMS (ESI^+): calcd for $C_{36}H_{45}N_4O_{10}$ [M + H^+] 693.3130; found 693.3118.

Compound 1c: Purified by flash chromatography (MeCN/H_2O, from 30:70 to 90:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 and 1.48 (2× s, 9 H), 1.50 and 1.52 (2× s, 9 H), 2.77 and 2.90 (2× d, J = 12.9 Hz, 1 H), 3.17 and 3.21 (2× s, 3 H), 3.38 (dd, J = 9.3, 12.9 Hz, 1 H), 3.50–3.66 (m, 2 H), 3.76 (s, 3 H), 4.83 (br. s, 1 H), 5.08–5.18 (m, 1 H), 6.64–6.75 (m, 3 H), 6.82 (t, J = 7.6 Hz, 1 H), 7.03–7.14 (m, 4 H), 7.24–7.31 (m, 1 H), 7.57 (dd, J = 7.6, 7.8 Hz, 1 H), 7.66–7.79 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4 (t), 28.2 (3× q), 28.3 (3× q), 38.8 (t), 52.1 (q), 52.6 (d), 52.8 (q), 59.3 (d), 72.4 (s), 79.6 (d), 79.7 (s), 82.0 (s), 110.4 (s), 111.4 (d), 119.2 (d), 119.9 (d), 122.3 (d), 123.1 (d), 123.4 (2× d), 124.4 (d), 124.7 (d), 125.0 (d), 128.9 (s), 129.7 (s), 130.8 (d), 131.7 (s), 134.0 (s and 2× d), 134.7 (s), 143.5 (s), 151.8 (2× s), 167.2 (s), 167.4 (s), 169.4 (s), 171.0 (s) ppm. IR (KBr): $\tilde{\nu}$ = 2977, 1716, 1390, 1255, 1158, 1019, 739, 721 cm^{-1}. HRMS (ESI^+): calcd for $C_{42}H_{45}N_4O_{10}$ [M + H^+] 765.3130; found 765.3091.

Compound 1d: Purified by flash chromatography (hexane/EtOAc, from 90:10 to 50:50); *endo*/*exo* (69:31) mixture. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 2.80 (d, J = 13.0 Hz, 1 H), 3.16 and 3.20 (2× s, 3 H), 3.37 (dt, J = 9.3, 13.0 Hz, 1 H), 3.49–3.68 (m, 2 H), 3.76 (s, 3 H), 4.88 (t, J = 10.6 Hz, 1 H), 5.07–5.30 (m, 3 H), 6.62–6.89 (m, 3 H), 7.02–7.10 (m, 4 H), 7.26–7.36 (m, 6 H), 7.54–7.61 (m, 1 H), 7.66 (dd, J = 3.1, 5.5 Hz, 1 H), 7.70 (dd, J = 3.1, 5.5 Hz, 1 H), 7.74 (dd, J = 3.1, 5.5 Hz, 1 H), 7.76 (dd, J = 3.1, 5.5 Hz, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 24.4 (t), 28.1 (3× q), 38.3 (t), 52.2 (q), 52.5 (d), 52.8 (q), 59.4 (d), 67.5 (t), 72.4 (s), 79.7 (d), 82.2 (s), 110.5 (s), 111.3 (d), 119.2 (d), 120.0 (d), 122.4 (2× d), 123.4 (4× d), 124.6 (d), 127.8 (d), 128.0 (d), 128.4 (3× d), 129.7 (s), 130.9 (d), 131.6 (s), 134.0 (2× d), 134.7 (s), 136.2 (s), 143.2 (s), 143.4 (s), 151.8 (s), 167.2 (s), 167.3 (s), 169.4 (s), 169.4 (s), 170.6 (s) ppm. IR (KBr): $\tilde{\nu}$ = 2952, 1716, 1389, 1255, 1158, 1020, 721 cm^{-1}. HRMS (ESI): calcd for $C_{45}H_{42}N_4O_{10}Na$ [M + Na^+] 821.2799; found 821.2804.

Compound 1e: Purified by flash chromatography (hexane/EtOAc, from 70:30 to 60:40). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.81–2.95 (m, 1 H), 2.98 (d, J = 13.4 Hz, 1 H), 3.07 (ddd, J = 5.0, 5.4, 14.8 Hz, 1 H), 3.27 (s, 3 H), 3.57 and 3.63 (2× s, 3 H), 3.62–3.68 (m, 1 H), 4.06–4.17 and 4.59–4.67 (2× m, 1 H), 4.74–4.82 and 5.27–5.33 (2× m, 1 H), 4.50–4.57 (m, 3 H), 4.96–5.08 (m, 1 H), 5.09–5.30 (m, 3 H), 5.80–5.96 (m, 1 H), 6.32 and 6.43 (2× s, 1 H), 6.80 and 6.93 (2× d, J = 13.7 Hz, 1 H), 7.10 (dd, J = 7.6, 8.1 Hz,

1 H), 7.12–7.18 (m, 2 H), 7.21 (br. s, 1 H), 7.37 (br. s, 1 H), 7.39–7.49 (m, 4 H), 7.52–7.59 (m, 1 H), 7.62 (dd, J = 2.9, 8.1 Hz, 1 H), 7.86 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.7 and 27.8 (t), 37.9 (t), 52.3 (q), 52.6 (q), 54.1 and 54.4 (d), 59.4 and 60.1 (d), 65.8 (t), 72.9 and 74.0 (s), 74.6 and 75.3 (t), 81.0 and 81.7 (d), 94.8 and 95.3 (s), 109.3 (s), 110.9 (d), 117.8 and 117.9 (t), 119.7 (d), 119.8 (d), 120.5 (d), 122.8 (d), 124.0 and 124.2 (d), 124.8 (d), 125.8 (d), 126.2 (d), 126.5 (s), 129.7 (d), 130.2 (s), 130.5 (s), 131.5 (d), 132.1 (d), 132.6 (d), 133.3 (d), 133.8 and 133.9 (s), 143.0 and 143.1 (s), 147.3 (s), 151.6 and 152.6 (s), 155.4 and 155.5 (s), 169.9 (s), 171.9 and 172.0 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3369, 2953, 1733, 1545, 1402, 1368, 1231, 1174, 1055, 852, 740, 580 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{37}H_{35}N_5O_{12}SCl_3$ [M + H$^+$] 878.1063; found 878.1059.

Compound 1f: Purified by flash chromatography (MeCN/H_2O, from 0:100 to 70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 and 1.34 (2× s, 9 H), 2.74–3.11 (m, 3 H), 3.27 (s, 3 H), 3.49–3.68 (m, 1 H), 4.45 (br. s, 1 H), 4.49–4.58 (m, 2 H), 4.59–4.84 (m, 2 H), 5.02 (br. s, 1 H), 5.09–5.33 (m, 3 H), 5.79–5.96 (m, 1 H), 6.36 and 6.46 (2× s, 1 H), 6.82 and 6.94 (2× d, J = 18.7 Hz, 1 H), 7.04–7.25 (m, 4 H), 7.29–7.58 (m, 6 H), 7.62 (d, J = 8.3 Hz, 1 H), 7.75–7.97 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8 and 28.0 (3× q), 27.9 (t), 37.9 (t), 52.6 (q), 54.4 and 54.6 (d), 59.4 (d), 65.7 (t), 74.6 (s), 75.3 (t), 81.6 (s), 82.2 (d), 109.5 (s), 110.8 (d), 117.8 (t), 119.8 (d), 120.2 (d), 120.5 (d), 122.7 (d), 124.2 (d), 124.6 (d), 125.8 (d), 126.3 (s), 126.7 (d), 129.7 (d), 130.5 (s), 131.7 (d), 132.1 (d), 132.7 (d), 133.3 (d), 133.7 (s), 137.9 (s), 143.1 (s), 147.4 (s), 155.6 (s), 155.7 (s), 169.9 (s), 170.6 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3419, 2979, 1733, 1545, 1368, 1230, 1173, 1129, 1055, 740, 581 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{40}H_{41}N_5O_{12}SCl_3$ [M + H$^+$] 920.1538; found 920.1578.

Compound 1g: Purified by flash chromatography (hexane/EtOAc, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.81–0.88 (m, 6 H), 1.00–1.12 (m, 1 H), 1.31 (s, 9 H), 1.39 (br. s, 1 H), 1.72–1.82 (m, 1 H), 2.67 (dd, J = 4.7, 14.7 Hz, 1 H), 2.82 (d, J = 13.3 Hz, 1 H), 3.08 (dd, J = 5.9, 14.7 Hz, 1 H), 3.21 (s, 3 H), 3.50 (m, 1 H), 3.83 (s, 3 H), 3.89 (dd, J = 6.6, 8.4 Hz, 1 H), 4.54 (m, 2 H), 4.64 (m, 1 H), 4.92 (br. s, 1 H), 5.21 (d, J = 10.5 Hz, 1 H), 5.26–5.34 (m, 2 H), 5.83 (br. s, 1 H), 5.84–5.96 (m, 1 H), 6.10 (d, J = 7.7 Hz, 1 H), 6.70 (br. s, 1 H), 6.90 (t, J = 7.8 Hz, 2 H), 7.15 (br. s, 2 H), 7.16–7.22 (m, 2 H), 7.23–7.35 (m, 4 H), 7.50 (t, J = 7.3 Hz, 2 H), 7.77 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4 (q), 15.3 (q), 24.7 (t), 27.6 (t), 28.0 (3× q), 37.2 (t), 37.8 (d), 52.3 (q), 53.3 (q and d), 59.2 (d), 59.5 (d), 65.8 (t), 73.4 (s), 81.9 (s), 82.1 (d), 109.2 (s), 110.9 (d), 117.7 (t), 119.9 (2× d), 120.5 (d), 122.7 (d), 124.3 (d), 125.7 (d), 126.4 (2× d), 126.7 (d), 128.5 (2× d), 130.3 (s), 130.6 (s), 131.7 (d), 132.2 (d), 132.7 (d), 133.5 (s), 138.2 (s), 143.2 (s), 154.8 (s), 155.9 (s), 170.1 (s), 170.5 (s), 170.6 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3367, 2954, 1721, 1447, 1363, 1170 cm^{-1}. HRMS (ESI): calcd for $C_{45}H_{54}N_5O_{11}S$ [M + H$^+$] 872.3541; found 872.3557.

Compound 1h: Purified by flash chromatography (hexane/EtOAc, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (dd, J = 9.5, 5.3 Hz, 1 H), 2.79 (d, J = 13.3 Hz, 1 H), 3.03–3.14 (m, 1 H), 3.20 (s, 3 H), 3.42–3.54 (m, 1 H), 3.58–3.68 (m, 6 H), 3.84 (s, 3 H), 4.42–4.57 (m, 1 H), 4.91 (br. s, 1 H), 5.10 (d, J = 8.1 Hz, 1 H), 5.73 (s, 1 H), 6.71 (br. s, 1 H), 6.87 (t, J = 7.5 Hz, 2 H), 7.12–7.35 (m, 5 H), 7.43–7.58 (m, 3 H), 7.80 (br. d, J = 7.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (t), 37.5 (t), 52.5 (3× q), 53.5 (q), 54.8 (d), 59.4 (d), 73.6 (s), 82.1 (d), 109.4 (s), 111.2 (d), 119.8 (d), 120.2 (d), 120.7 (d), 123.0 (d), 124.3 (d), 124.5 (s), 125.8 (s), 126.6 (2× d), 126.8 (d), 128.7 (2× d), 130.5 (s), 132.1 (2× d), 132.4 (d), 133.7 (s), 138.3 (s), 143.5 (s), 156.5 (s), 170.6 (s), 172.3 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3328, 2964, 1722, 1676, 1448, 1368, 1170 cm^{-1}. HRMS (ESI): calcd for $C_{34}H_{35}N_4O_{10}S$ [M + H$^+$] 691.2074; found 691.2079.

Compound 1i: Purified by flash chromatography (MeCN/H_2O, from 30:70 to 50:50). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (m, 6 H), 1.07 (m, 1 H), 1.18 (s, 9 H), 1.40 (s, 10 H), 1.80 (m, 1 H), 2.80 (m, 2 H), 3.10 (dd, J = 5.9, 14.6 Hz, 1 H), 3.50 (dd, J = 10.1, 13.4 Hz, 1 H), 3.81 (s, 3 H), 3.85 (m, 1 H), 4.41 (dd, J = 5.7, 13.2 Hz, 1 H), 4.51 (dd, J = 5.7, 13.2 Hz, 1 H), 4.70–4.87 (m, 2 H), 5.10 (br. s, 1 H), 5.20 (m, 2 H), 5.70 (m, 1 H), 5.78 (br. s, 1 H), 6.20 (d, J = 7.0 Hz, 1 H), 6.65 (br. s, 1 H), 6.85 (t, J = 7.6 Hz, 2 H), 7.25 (m, 8 H), 7.50 (m, 2 H), 7.80 (d, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.6 (q), 15.4 (q), 24.7 (t), 27.7 (3× q), 28.2 (t), 28.4 (3× q), 31.5 (q), 36.6 (q), 37.3 (t), 37.7 (d), 53.2 (d), 59.1 (d), 60.0 (d), 66.0 (t), 79.8 (s), 82.1 (d), 82.3 (s), 109.0 (d), 111.1 (d), 118.8 (t), 119.6 (d), 120.1 (s), 120.6 (d), 122.8 (d), 124.4 (d), 126.0 (d), 126.5 (d), 126.6 (d), 128.6 (2× d), 130.4 (d), 131.0 (s), 131.4 (d), 131.7 (d), 132.3 (d), 133.7 (s), 138.3 (s), 141.7 (s), 143.2 (s), 145.0 (s), 155.6 (s), 162.7 (s), 168.8 (s), 171.0 (s), 171.3 (s) ppm. IR (KBr): $\tilde{\nu}$ = 3323, 2965, 2929, 1716, 1448, 1367, 1171 cm^{-1}. HRMS (ESI): calcd for $C_{48}H_{60}N_5O_{11}S$ [M + H$^+$] 914.4010; found 914.3986.

Compound 1j: Purified by flash chromatography (hexane/EtOAc, 70:30). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–1.03 (m, 6 H), 1.13 (dd, J = 3.2, 6.7 Hz, 2 H), 1.54 (s, 9 H), 1.56 (s, 9 H), 2.52 (br. s, 1 H), 2.68–2.90 (m, 1 H), 2.97–3.15 (m, 1 H), 3.54–3.66 (m, 2 H), 3.77 (s, 3 H), 3.94–4.07 (m, 1 H), 4.49–4.73 (m, 3 H), 5.08–5.31 (m, 3 H), 5.75–5.90 (m, 1 H), 6.50 (d, J = 7.7 Hz, 1 H), 6.65 (d, J = 11.2 Hz, 1 H), 6.75 (d, J = 9.2 Hz, 1 H), 6.87–7.18 (m, 5 H), 7.33–7.41 (m, 1 H), 7.61 (dd, J = 6.1, 7.4 Hz, 1 H), 7.66–7.83 (m, 5 H), 7.87–8.01 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.7 and 11.3 (q), 15.8 and 16.8 (q), 24.3 (t), 25.8 and 27.4 (t), 28.2 (6× q), 34.1 and 34.4 (d), 39.9 (t), 52.2 and 52.3 (d), 52.8 (q), 56.8 and 58.2 (d), 61.2 (d), 61.5 (s), 66.3 (t), 78.4 (d), 78.7 (s), 83.1 (2× s), 109.7 (s), 110.7 (d), 111.0 (d), 116.0 and 116.1 (d), 118.8 (t), 119.4 (d), 120.3 (d), 122.8 (d), 123.3 (d), 123.4 (d), 123.5 and 123.6 (s), 124.5 (2× d), 126.4 (s), 129.9 (s), 131.4 (d), 131.5 (d), 131.7 (s), 134.1 (2× d), 134.3 (s), 134.4 (s), 151.2 (s), 167.1 (s), 167.3 (s), 168.0 (s), 168.1 (s), 169.3 (2× s) ppm. IR (KBr): $\tilde{\nu}$ = 3413, 2969, 1718, 1483, 1455, 1388, 1253, 1162, 1019, 739, 720 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{46}H_{49}N_5O_{11}$ [M – tBu] 847.3429; found 847.3658.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data of compounds **3a**–**p**, **5**, and **8** and copies of the ^{1}H and ^{13}C NMR spectra of **1a**–**j**, **3g**, **5** and **8**.

Acknowledgments

This study was partially supported by Centro de Investigación Científica y Tecnológica (CICYT) (grant number CTQ2009-07758), the Generalitat de Catalunya (2009SGR 1024), the Institute for Research in Biomedicine, and the Barcelona Science Park. P. R. S. received a PhD fellowship from the Institute for Research in Biomedicine (02/06-IRB).

[1] P. Ruiz-Sanchis, S. A. Savina, F. Albericio, M. Álvarez, *Chem. Eur. J.* **2011**, *17*, 1388–1408.
[2] B. Witkop, *Heterocycles* **1998**, *49*, 9–27.
[3] a) J. S. Carlé, C. Christophersen, *J. Am. Chem. Soc.* **1979**, *101*, 4012–4013; b) J. S. Carlé, C. Christophersen, *J. Org. Chem.* **1980**, *45*, 1586–1589; c) J. S. Carlé, C. Christophersen, *J. Org. Chem.* **1981**, *46*, 3440–3443; d) M. V. Laycock, J. L. C. Wright, J. A. Findlay, A. D. Patil, *Can. J. Chem.* **1986**, *64*, 1312–1316; e) P. B. Holst, U. Anthoni, C. Christophersen, P. H. Nielsen, *J. Nat. Prod.* **1994**, *57*, 997–1000; f) S. J. Rochfort, S. Moore, C.

Craft, N. H. Martin, R. M. Van Wagoner, J. L. C. Wright, *J. Nat. Prod.* **2009**, *72*, 1773–1781.
[4] a) M. Kusano, G. Sotoma, H. Koshino, J. Uzawa, M. Chijimatsu, S. Fujioka, T. Kawano, Y. Kimura, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2823–2826; b) Y. Kimura, A. Sawada, M. Kuramata, M. Kusano, S. Fujioka, T. Kawano, A. Shimada, *J. Nat. Prod.* **2005**, *68*, 237–239; c) L. Du, X. Yang, T. Zhu, F. Wang, X. Xiao, H. Park, Q. Gu, *Chem. Pharm. Bull.* **2009**, *57*, 873–876.
[5] a) S. Ohmomo, T. Sato, T. Utagawa, M. Abe, *Agric. Biol. Chem.* **1975**, *39*, 1333–1334; b) S. Ohmomo, T. Utagawa, M. Abe, *Agric. Biol. Chem.* **1977**, *41*, 2097–2098; c) S. Ohmomo, K. Oguma, T. Ohashi, M. Abe, *Agric. Biol. Chem.* **1978**, *12*, 2387–2389; d) L. Du, D. Li, T. Zhu, S. Cai, F. Wang, X. Xiao, Q. Gu, *Tetrahedron* **2009**, *65*, 1033–1039.
[6] R. K. Duke, R. D. Allan, G. A. R. Johnston, K. N. Mewett, A. D. Mitrovic, C. C. Duke, T. W. Hambley, *J. Nat. Prod.* **1995**, *58*, 1200–1208.
[7] N. K. Hart, S. R. Johns, J. A. Lamberton, R. E. Summons, *Aust. J. Chem.* **1974**, *27*, 639–646.
[8] a) V. Jannic, F. Gueritte, O. Laprevote, L. Serani, M.-T. Martin, T. Sévenet, P. Potier, *J. Nat. Prod.* **1999**, *62*, 838–843; b) L. Verotta, T. Pilati, M. Tato, E. Elisabetsky, T. A. Amador, D. S. Nunes, *J. Nat. Prod.* **1998**, *61*, 392–396; c) F. Guéritte-Voegelein, T. Sévenet, J. Pusset, M.-T. Adeline, B. Gillet, J.-C. Beloeil, D. Guénard, P. Potier, R. Rasolonjanahary, C. Kordon, *J. Nat. Prod.* **1992**, *55*, 923–930; d) F. Libot, C. Miet, N. Kunesch, J. E. Poisson, J. Pusset, T. Sévenet, *J. Nat. Prod.* **1987**, *50*, 468–473; e) K. P. Parry, G. F. Smith, *J. Chem. Soc. Perkin Trans. 1* **1978**, 1671–1682.
[9] H. Takayama, I. Mori, M. Kitajima, N. Aimi, N. H. Lajis, *Org. Lett.* **2004**, *6*, 2945–2948.
[10] a) S. A. Waksman, E. Bugie, *J. Bacteriol.* **1944**, *48*, 527–530; b) W. B. Geiger, J. E. Conn, S. A. Waksman, *J. Bacteriol.* **1944**, *48*, 531–536; c) W. B. Geiger, *Arch. Biochem.* **1949**, *21*, 125–131; d) S. Safe, A. Taylor, *J. Chem. Soc. Perkin Trans. 1* **1972**, 472–479; e) A. G. McInnes, A. Taylor, J. A. Walter, *J. Am. Chem. Soc.* **1976**, *98*, 6741–6741; f) T. Kikuchi, S. Kadota, K. Nakamura, A. Nishi, T. Taga, T. Kaji, K. Osaki, K. Tubaki, *Chem. Pharm. Bull.* **1982**, *30*, 3846–3848; g) G.-Y. Li, B.-G. Li, T. Yang, J.-F. Yan, G.-Y. Liu, G.-L. Zhang, *J. Nat. Prod.* **2006**, *69*, 1374–1376.
[11] a) Y. Nakao, B. K. S. Yeung, Y. W. Yoshida, P. J. Scheurer, *J. Am. Chem. Soc.* **1995**, *117*, 8271–8272; b) B. K. S. Yeung, Y. Nakao, R. B. Kinnel, J. R. Carney, W. Y. Yoshida, P. J. Scheuer, M. Kelly-Borges, *J. Org. Chem.* **1996**, *61*, 7168–7173; c) Y. Nakao, J. Kuo, W. Y. Yoshida, M. Kelly, P. J. Scheuer, *Org. Lett.* **2003**, *5*, 1387–1390.
[12] a) Y. Matsuda, M. Kitajima, H. Takayama, *Org. Lett.* **2008**, *10*, 125–128; b) T. Newhouse, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887; c) N. Takahashi, T. Ito, Y. Matsuda, N. Kogure, M. Kitajima, H. Takayama, *Chem. Commun.* **2010**, *46*, 2501–2503; d) T. Newhouse, C. A. Lewis, K. J. Eastman, P. S. Baran, *J. Am. Chem. Soc.* **2010**, *132*, 7119–7137.
[13] T. Newhouse, C. A. Lewis, P. S. Baran, *J. Am. Chem. Soc.* **2009**, *131*, 6360–6361.
[14] K. Foo, T. Newhouse, I. Mori, H. Takayama, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, *50*, 2716–2719.
[15] V. R. Espejo, J. D. Rainier, *J. Am. Chem. Soc.* **2008**, *130*, 12894–12895.
[16] V. R. Espejo, J. D. Rainier, *Org. Lett.* **2010**, *12*, 2154–2157.
[17] V. R. Espejo, J. D. Rainier, *J. Am. Chem. Soc.* **2010**, *132*, 8282–8284.
[18] M. Taniguchi, T. Hino, *Tetrahedron* **1981**, *37*, 1487.
[19] C. Silva-López, C. Pérez-Balado, P. Rodríguez-Granja, A. R. de Lera, *Org. Lett.* **2008**, *10*, 77–80.
[20] Column: Waters XBridge C_{18} (75 × 4.6 mm, 2.5 μm); MeCN/H_2O (from 30:70 to 100:0 in 8 min).
[21] Several reaction conditions were tested to remove the Moc group from methyl N^1-(methoxycarbonyl)-N^8-(phenylsulfonyl)-HPI-2-carboxylate (**S6**; see the Supporting Information): the reagents comprised LiOH, LiSBn, $LiSCH_2CH_2OH$, or TMSI; the solvents tested were THF, H_2O, 1,4-dioxane, MeOH, and HMPA; and the temperatures ranged from room temp. to solvent reflux temperature. Several of these tests were performed with microwave heating.
[22] a) M. Bruncko, D. Crich, R. Samy, *J. Org. Chem.* **1994**, *59*, 5543–5549; b) M. Kawahara, A. Nishida, M. Nakagawa, *Org. Lett.* **2000**, *2*, 675–678.
[23] a) T. M. Kamenecka, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 3164–3166; *Angew. Chem. Int. Ed.* **1998**, *37*, 2993–2995; b) T. M. Kamenecka, S. J. Danishefsky, *Angew. Chem.* **1998**, *110*, 3166–3168; *Angew. Chem. Int. Ed.* **1998**, *37*, 2995–2998.
[24] a) N. H. Martin, N. W. Allen III, K. D. Moore, L. Vo, *J. Mol. Struct.* **1998**, *454*, 161–166; b) D. Crich, A. Banerjee, *Acc. Chem. Res.* **2007**, *40*, 151–161.
[25] The 3D models of Br-HPI *endo*-**3g** and *exo*-**3g** were calculated with Gaussian® 03W V 6.0 (Gaussian Inc.) and built with ChemBio3D V 11.0 (CambridgeSoft) .
[26] Use of base/solvent pairs such as NaH/THF, NaHMDS/THF, K*t*BuO/MeCN, or proton sponge/THF did not provide better yields.
[27] V. R. Espejo, X.-B. Li, J. D. Rainier, *J. Am. Chem. Soc.* **2010**, *132*, 8282–8284.

Received: July 20, 2011
Published Online: November 22, 2011

