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Total Synthesis of Endolides A and B

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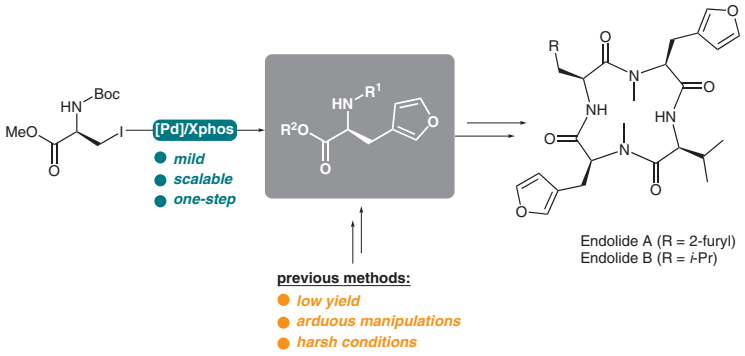

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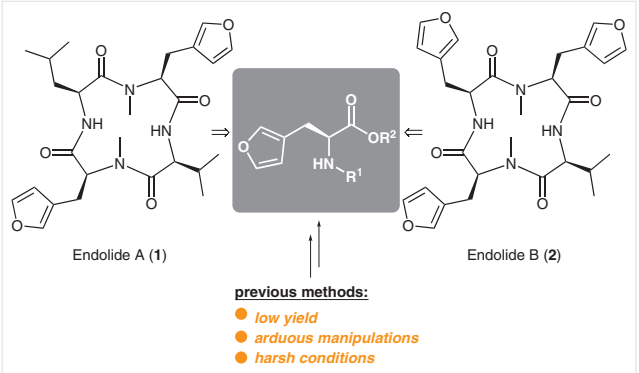
Abstract The total synthesis of endolides A and B has been achieved in a concise and highly stereoselective fashion (12 steps; 16.2 and 16.0% overall yield, respectively). Key features of the route include a modified Negishi coupling between 3-bromofuran and an organozinc reagent derived from an iodoalanine derivative for the synthesis of a 3-(3-furyl)alanine derivative, and a judicious choice of reaction conditions to overcome the conformational constraints placed by converting a linear peptide into the corresponding macrocycle.

Key words total synthesis, endolides, Negishi coupling, furylalanine, Buchwald phosphine ligands, peptide macrocycles



Scheme 1 Structures and synthetic challenges of endolides A and B

Marine-derived cyclopeptides exhibit a diverse range of biological activities and usually show cell permeability, metabolic stability, and easy-to-control variability; they are therefore promising lead structures for the development of new therapeutic agents. Endolides A and B (Scheme 1) were isolated from a culture broth of marine-derived fungus *Stachylidium* sp.[1] The absolute configuration of the noncanonical 3-(3-furyl)alanine moiety was established through a combination of an advanced Marfey method coupled with crystallographic data for endolide A. On the basis of biosynthetic considerations, the 3-(3-furyl)alanine moiety of endolide B was assumed to possess the same configuration as that of endolide A. The endolides belong to one of seven families of naturally occurring cyclotetrapeptides containing N-methylated residues.[2]

The N-methylated amide bond present in endolides is a feature that increases their conformational rigidity and, additionally, might lead to improved pharmacological properties. Endolide A exhibited a high affinity to the vasopressin receptor 1A with a K_i of 7.04 μM, whereas endolide B showed affinity towards the serotonin receptor $5HT_{2b}$ with a K_i of 0.77 μM. While our work was underway, Brimble and co-workers reported a solid-phase synthesis of endolides A and B.[3] As part of a program directed toward the synthesis, structural modification studies, and biological evaluation of marine-derived macrocycles,[4] we report total syntheses of endolides A and B.

The principal challenges associated with the total syntheses of endolides A and B are the preparation of the nonproteinogenic L-3-(3-furyl)alanine moiety and the formation of the strained 12-membered macrocycle. The challenge in the synthesis of the nonproteinogenic L-3-(3-furyl)alanine moiety arises from the difficulty in controlling the reactivities of 3-furyl-derived reagents. This issue has led the reported syntheses being markedly ineffective.[5] Uemura and co-workers reported the first asymmetric synthesis of an L-3-(3-furyl)alanine derivative en route

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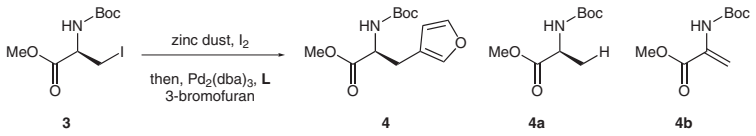
to rhizonin A; however, laborious synthetic steps detracted from the overall efficiency of their route. The Cobb group developed an approach for the construction of five-membered heteroaromatic amino acids based on the Negishi coupling process. Although the construction of 3-(3-furyl)alanine derivative could be achieved in a straightforward fashion, disappointing low yields ultimately thwarted their efforts. Rhodium-catalyzed asymmetric hydrogenation of furyl-substituted dehydroamino acid derivatives is more step economical, but often necessitated high reaction pressures and is expensive. The pursuit of endolides prompted us to explore a cost-effective method to access the challenging 3-(3-furyl)alanine derivative. Modern developments in phosphine ligands[6] for cross-coupling reactions spurred us to seek a catalytic system for the Negishi coupling to address the problem.

The system was surveyed by using the iodoalanine derivative **3**. With Sphos [2-(dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl][7] as the ligand, variations from Cobb's condition were screened, resulting in a slight improvement in the yield.[8] Formation of byproducts derived from either β-hydride elimination or deiodination served as major hurdles. Although the nature of the influence of ligand structure on the observed chemoselectivity was not yet fully understand, we elected to investigate the influence of the steric and electronic properties of various phosphine ligands on the efficiency of the Negishi coupling reaction to access the desired product in an acceptable yield for our total synthesis. As shown in Table 1, several bidentate ligands and $Pd(PPh_3)_4$ proved to be ineffective (Table 1, entries 2–4 and 10). When Ruphos [2-(dicyclohexylphosphino)-2′,6′-diisopropoxybiphenyl] was employed, the yields of byproducts **4a** and **4b** were similar (17%) and the yield of the desired product **4** increased to 58% (entry 5). Spurred by these findings, as well as by Buchwald's pioneering work in this area[6], we opted to carry out further screening of ligands (entries 6–9). Gratifyingly, it was found that the Xphos [2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl] was the most effective ligand for the coupling reaction, and the 3-(3-furyl)alanine methyl ester **4** was obtained in 71% yield without any decrement of the yield when the reaction was conducted on a multigram scale. In addition, we believe this catalytic system can also be applied to diverse scaffolds with embedded heteroaromatic amino acids.

With a practical route to amino ester **4** in hand, we set out to pursue the total synthesis of endolides. Our initial synthetic route to endolide A (**1**) involved the construction of tetrapeptide **12** from dipeptides **9** and **11** (Scheme 2). Thus, saponification of the 3-(3-furyl)alanine methyl ester **4** with aqueous lithium hydroxide in THF provided the necessary carboxylic acid, which then underwent a selective N-methylation by NaH and MeI to afford **5** in 91% yield over

Table 1 Synthesis of an L-3-(3-Furyl)alanine Derivative[a]

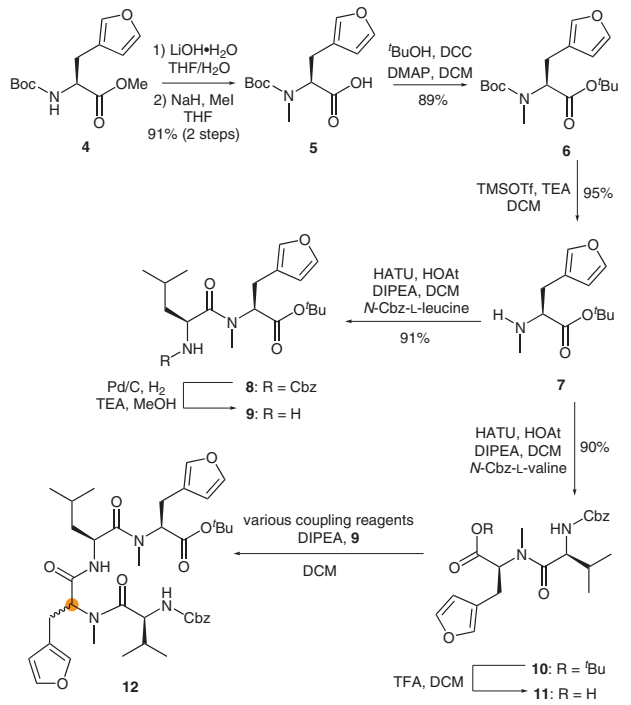


3 4 4a 4b

Entry	Ligand	4	4a	4b
1	Sphos	34%	17%	17%
2	dppf[b]	0	93%	7%
3	dppp[c]	0	71%	29%
4	Xantphos[d]	0	98%	2%
5	Ruphos	58%	17%	17%
6	JohnPhos[e]	39%	18%	18%
7	^{t}BuXphos[f]	20%	14%	66%
8	**Xphos**[g]	**71%**	**22%**	**7%**
9	Brettphos[h]	30%	41%	30%
10	PPh_3[i]	0	90%	10%

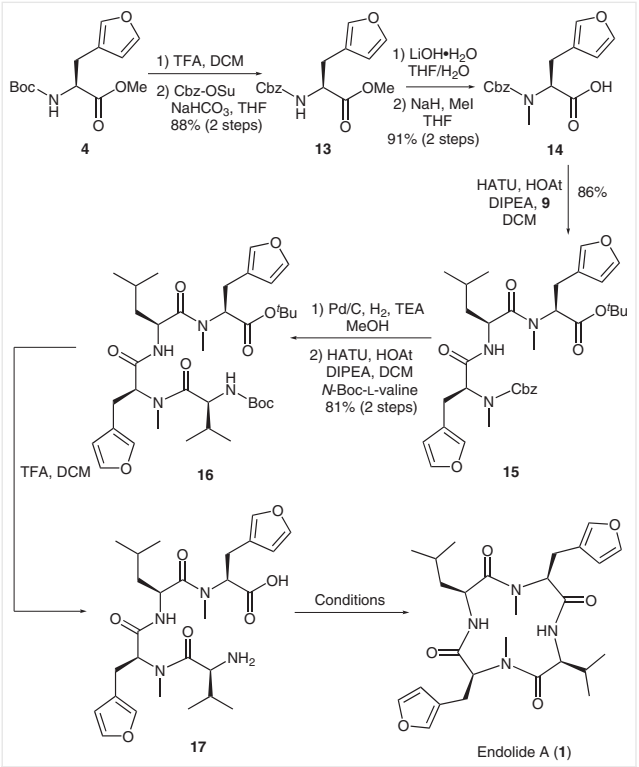
[a] Reaction conditions: (i) Zn dust (4.0 equiv), heated under vacuum with a heat gun, 20 min; (ii) I_2 (0.1 equiv), DMF, 70 °C, 20 min, under Ar; **3** (1.0 equiv), 50 °C, 20 min; (iii) 3-bromofuran (3.0 equiv), $Pd_2(dba)_3$ (0.1 equiv), ligand (0.4 equiv), 50 °C, 5 h, then 25 °C, 20 h.
[b] 1,1′-Bis(diphenylphosphino)ferrocene.
[c] $Ph_2P(CH_2)_3PPh_2$.
[d] 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.
[e] 2-(Di-*tert*-butylphosphino)biphenyl.
[f] 2-Di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl.
[g] Reaction performed on a 5 g scale.
[h] 2-(Dicyclohexylphosphino)-3,6-dimethoxy-2′,4′,6′-triisopropylbiphenyl
[i] $Pd(PPh_3)_4$ was used.

the two steps. Acid **5** was treated with *tert*-butanol, DCC, and DMAP in dichloromethane to generate the *tert*-butyl ester **6** in 89% yield. The Boc carbamate functionality of **6** was cleaved by using the Ohfune procedure[9] to provide amino ester **7** in 95% yield. Amino ester **7** reacted with *N*-Cbz-L-leucine and *N*-Cbz-L-valine in the presence of 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol (HOAt) to afford dipeptides **8** and **10** in yields of 91 and 90%, respectively. Unfortunately, condensations of dipeptide acid **11** with trifluoroacetate salts of dipeptide **9** employing various coupling reagents provided tetrapeptide **12** as mixtures of diastereomers. The substantial epimerization of the coupling product presumably arises from the readily epimerizable L-3-(3-furyl)-*N*-methylalanine.



Scheme 2 Attempted synthesis of tetrapeptide **12**

To circumvent this problem, an alternative route for the preparation of the linear tetrapeptide was considered (Scheme 3). Thus, acidic cleavage of the Boc group of **4** followed by reprotection of the resultant amine as its Cbz carbamate provided **13** in 88% yield over two steps. Saponification of methyl ester **13**, followed by a selective N-methylation with NaH and MeI gave **14** in 91% yield. This was coupled with the previously synthesized amine **9** by the action of HATU, HOAt, and DIPEA to give tripeptide **15** in 86% yield. Hydrogenolysis of the Cbz group of tripeptide **15** provided the corresponding free amine, which was coupled with *N*-Boc-L-valine to afford the tetrapeptide **16** in 81% yield with preservation of stereochemical integrity. Simultaneous removal of the *tert*-butyl ester and Boc-protecting group was achieved by treatment of **16** with TFA in dichloromethane, giving the desired amino acid **17**, which was then submitted to macrolactamization.



Scheme 3 Attempted synthesis and cyclization of **17**

Much to our dismay, however, macrolactamization of **17** generally resulted in sluggish conversions when various coupling reagents were employed (Table 2). When the reaction was mediated by HATU, EDCI, BOPCl, (7-azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyAOP), or 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP)[10], none of the desired product could be isolated from the crude reaction mixture (Table 2, entries 1–5). Treatment of **17** with peptide-coupling reagents such as(benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP), pentafluorophenyl diphenylphosphinate (FDPP), or propylphosphonic acid anhydride (T_3P)[11] provided endolide A (**1**) in low isolated yields with low mass recovery (entries 6–8). We postulated that the reluctance of substrate **17** to undergo a macrolactamization might be due to unfavorable conformations that preclude macrocyclization.

Table 2 Macrolactamization of **17**

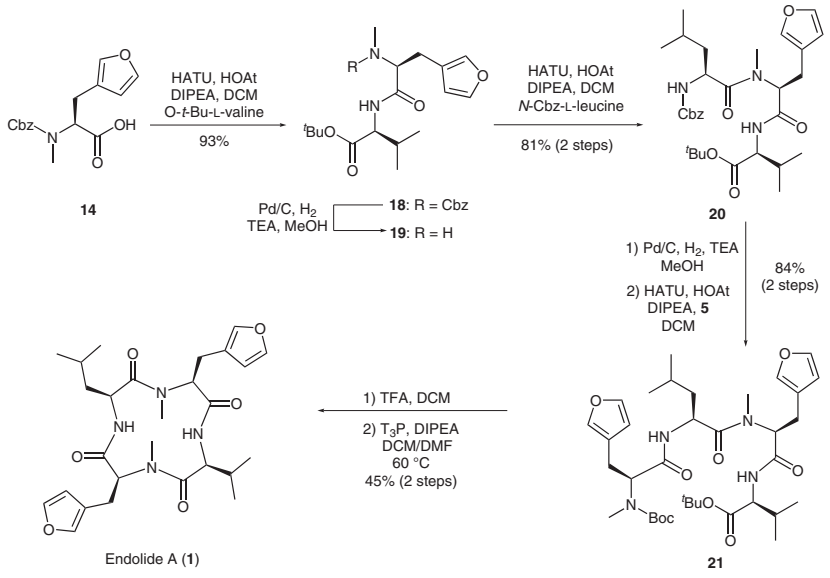
Entry	Conditions	Result
1	HATU, HOAt, DIPEA, DCM, rt	no product
2	EDCI, DIPEA, DCM, rt	no product
3	BOP-Cl, DIPEA, DCM, rt	trace
4	PyAOP, DIPEA, DCM, rt	trace
5	BEP, DIPEA, DCM, rt	trace
6	BOP, DIPEA, DCM, rt	8%
7	FDPP, DIPEA, DCM, rt	5%
8	T_3P, DIPEA, DCM, rt	9%

It is known that the cyclization of linear tetrapeptides can sometimes be sequence dependent.[3,12,13] We therefore devised an alternative macrolactamization process for the synthesis of endolide A (**1**). We hoped that the strategic placement of the L-3-(3-furyl)-*N*-methylalanine at the (*i* + 2) position of a potential β-turn structure would organize the cyclization precursor and result in more-favorable cyclization kinetics. Thus, acid **14** and *O*-*tert*-butyl-L-valine were coupled by using HATU/HOAt/DIPEA activation to furnish dipeptide **18** in 93% yield. Elongation of the peptide chain to the linear tetrapeptide **21** was accomplished by stepwise coupling of *N*-Cbz-Leucine and L-3-(3-furyl)-*N*-methyl-*N*-Boc-alanine (**5**) under the same HATU/HOAt/DIPEA activation conditions (Scheme 4). Simultaneous removal of the *tert*-butyl ester and Boc-protecting group was achieved by treatment of **21** with TFA in dichloromethane at room temperature to produce the desired amino acid, which was immediately activated by T_3P at 60 °C in the presence of DIPEA to afford endolide A (**1**) in 45% yield over two steps. It is worth mentioning that alternative reagents, including DPPA (0%) and HATU/HOAt (~20%), were less effective in promoting the macrocyclization.

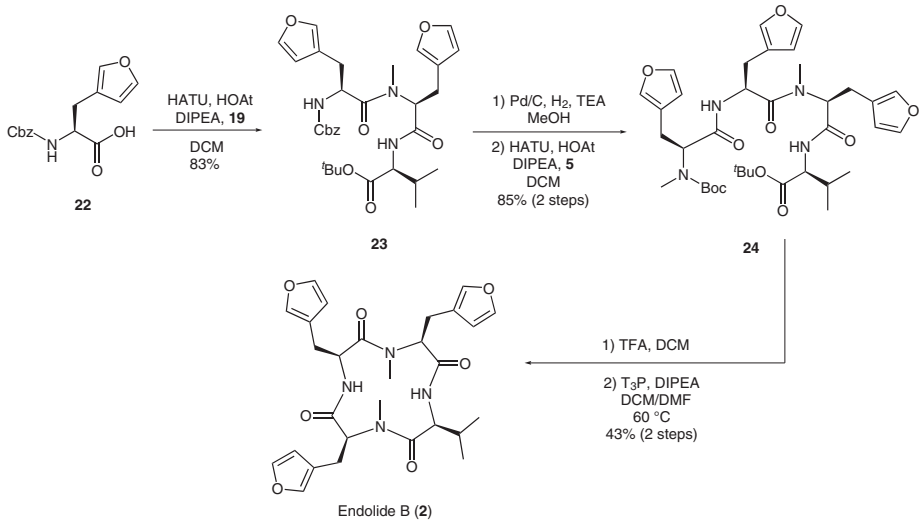
Encouraged by our successful construction of endolide A (**1**), we proceeded to synthesize endolide B (**2**) by following a similar strategy. In the event, L-3-(3-furyl)-*N*-Cbz-alanine (**22**), derived by saponification of the corresponding methyl ester (**13**), was transformed into the key macrolactamization precursor **24** in 70% overall yield by an identical strategy to that described for the synthesis of **21**, including Cbz deprotection and HATU-mediated condensation (Scheme 5). Upon acidic cleavage of the Boc and *tert*-butyl ester groups of **24**, the resulting amino acid was cyclized with T_3P and DIPEA at 60 °C to deliver endolide B (**2**) in 43% yield.

The spectral data for synthetic **1** and **2** (^1H and ^{13}C NMR and HRMS) were identical to those published for the natural products, thereby confirming the proposed structures of the natural products.

Natural endolides A (**1**) and B (**2**) had previously been shown to have affinity towards vasopressin receptor 1A (K_i = 7.04 μM) and the serotonin receptor 5-HT_{2B} (K_i = 0.77 μM), respectively, with **2** showing no affinity towards other serotonin subtypes[1] in a ligand-binding assay. For the first time, we tested synthetic samples of these two compounds in a functional cellular assay against the same two receptors in both agonist and antagonist mode at a concentration of 20 μM. Endolides A (**1**) and B (**2**) showed 13 and 16% inhibition (antagonist activity), respectively, relative to the controls of 5-HT_{2B} receptor. The compounds were not inhibitory against the V1a receptor in a cellular assay at 20 μM. To explain the previously demonstrated ligand-binding activity of **1** and **2**, it is possible that these compounds either bind to the receptors, but do not cause sufficient inhibition



Scheme 4 Synthesis of endolide A (**1**)



Scheme 5 Synthesis of endolide B (**2**)

to cause a functional response or they are unable to bind to the receptors efficiently in the cellular model at the concentration used.

In summary, we report total syntheses of endolides A and B in a concise and highly stereoselective fashion (12 steps; 16.2 and 16.0% overall yields, respectively).[14] Key features of the route include a modified Negishi coupling for the synthesis of a 3-(3-furyl)alanine moiety and a judicious choice of reaction conditions to surmount the conformational constraints involved in converting a linear peptide into the corresponding macrocycle. The synthetic route offers a general approach to access the remaining members of this class of natural products; it also opens the door to rapid syntheses of analogues to explore structure–function relationships that might lead to the discovery of endolide analogues with better cellular activities.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610736.

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(14) **Endolide A** (**1**)
White solid; yield: 44.0 mg (45% for 2 steps); R_f = 0.40 (EtOAc–hexanes, 1:1); $[\alpha]_{24}^{D}$ –181.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.89 (d, *J* = 9.6 Hz, 1 H), 7.80 (d, *J* = 8.6 Hz, 1 H), 7.53 (t, *J* = 1.7 Hz, 2 H), 7.44 (s, 1 H), 7.43 (s, 1 H), 6.39 (s, 1 H), 6.37 (s, 1 H), 4.68 (td, *J* = 8.8, 5.7 Hz, 1 H), 4.39 (dd, *J* = 11.7, 3.3 Hz, 1 H), 4.40–4.34 (m, 1 H), 4.31 (dd, *J* = 11.6, 3.2 Hz, 1 H), 3.40 (dd, *J* = 11.4, 2.9 Hz, 1 H), 3.37 (dd, *J* = 11.4, 2.9 Hz, 1 H), 2.96 (t, *J* = 11.6 Hz, 1 H), 2.92 (t, *J* = 11.6 Hz, 1 H), 2.79 (s, 3 H), 2.75 (s, 3 H), 2.21–2.07 (m, 1 H), 1.75–1.63 (m, 1 H), 1.62–1.47 (m, 1 H), 1.36–1.23 (m, 1 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.87 (d, *J* = 7.2 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 6 H). ^{13}C NMR (101 MHz, acetone-d_6): δ = 172.9, 172.1, 170.7, 170.3, 144.4, 144.3, 141.0, 141.0, 122.0, 121.9, 110.9, 110.8, 62.8, 62.6, 56.2, 49.2, 41.9, 30.5, 30.3, 30.1, 25.0, 24.4, 24.4, 23.2, 22.5, 20.7, 18.4. HRMS: *m/z* $[M + Na]^+$ Calcd for $C_{27}H_{38}N_4NaO_6$: 537.2689; found: 537.2679.

Endolide B (**2**)
White solid; yield: 44 mg (43% for 2 steps); R_f = 0.35 (EtOAc–hexanes, 1:1); $[\alpha]_{24}^{D}$ –180.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.92 (d, *J* = 9.7 Hz, 1 H), 7.80 (d, *J* = 9.6 Hz, 1 H), 7.52 (t, *J* = 1.7 Hz, 1 H), 7.47 (t, *J* = 1.8 Hz, 1 H), 7.42–7.40 (m, 3 H), 7.28 (s, 1 H), 6.36 (d, *J* = 0.9 Hz, 1 H), 6.34 (d, *J* = 1.0 Hz, 1 H), 6.30 (d, *J* = 1.0 Hz, 1 H), 4.86 (dt, *J* = 9.6, 6.7 Hz, 1 H), 4.41–4.32 (m, 2 H), 4.30 (dd, *J* = 11.7, 3.3 Hz, 1 H), 3.38 (dd, *J* = 15.2, 2.9 Hz, 1 H), 3.31 (dd, *J* = 15.6, 2.6 Hz, 1 H), 2.97 (d, *J* = 15.2 Hz, 1 H), 2.95 (dd, *J* = 15.0, 5.5 Hz, 1 H), 2.86 (d, *J* = 11.8 Hz, 1 H), 2.81 (s, 3 H), 2.73 (s, 3 H), 2.61 (dd, *J* = 14.8, 6.7 Hz, 1 H), 2.18–2.07 (m, 1 H), 0.85 (d, *J* = 7.0 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (101 MHz, acetone-d_6): δ = 172.5, 172.1, 170.7, 170.1, 144.4, 144.4, 143.2, 141.3, 141.0, 141.0, 122.0, 122.0, 121.7, 112.8, 111.0, 110.9, 62.8, 62.6, 56.2, 51.4, 30.6, 30.3, 30.1, 28.0, 24.7, 24.4, 20.8, 18.4. HRMS: *m/z* $[M + Na]^+$ Calcd for $C_{28}H_{34}N_4NaO_7$: 561.2325; found: 561.2306.