Total Synthesis of Largazole

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Abstract: The stereocontrolled total synthesis of largazole was accomplished, unambiguously confirming its structure. Key steps included the use of the Nagao thiazolidinethione auxiliary for a diastereoselective acetate aldol reaction, thiazoline–thiazole formation, and macrolactamization by use of the Mukaiyama reagent.

Key words: largazole, cyclodepsipeptide, total synthesis, antitumor, macrolactamization

Marine cyanobacteria have produced a wide variety of secondary metabolites,[1] many of which have demonstrated antiproliferative activity,[2] acute cytotoxic activity,[3] or have specific neurotoxic activity.[4] Their diversity in both biological activity and in structural complexity has made these natural products the focus of much work in recent years. The small quantities of compounds that are produced by many marine cyanobacteria have proven to be a severe obstacle for the development of promising new leads for the development of novel drugs.[5] In order to obtain significant amounts of these structurally interesting marine natural products, we[6] and other groups[7] have undertaken extensive programs towards their syntheses. In connection with our own proposed studies in the area of synthesis of anticancer natural products and our continuing interests in devising strategy toward analogue development, we herein report the total synthesis of largazole (**1**) that is amenable to analogue construction.

Largazole (**1**) was recently isolated from the Floridian marine cyanobacterium *Symploca* sp. by Luesch and coworkers.[8] Its structure was determined by a combination of chemical degradation, chiral chromatography, and spectroscopic analysis. Preliminary biological characterization indicated that largazole potently inhibited the growth of highly invasive transformed human mammary epithelial cells with nanomolar antiproliferative activity.[8] Furthermore, largazole has several interesting structural features including a thioester that involves the novel 3-hydroxy-7-mercaptohept-4-enoic acid unit and a substituted 4-methylthiazoline linearly fused to a thiazole.

There are three principal challenges associated with the synthesis of largazole: (1) the asymmetric construction of 3-hydroxy-7-mercaptohept-4-enoic acid, (2) the formation of a 16-membered cyclic depsipeptide, and (3) the synthetic manipulation of the β-hydroxyl-γ,δ-unsaturated ester while avoiding β-elimination, protecting group migration, and intramolecular cyclization.

Bearing this analysis in mind, we devised a retrosynthetic strategy toward largazole (**1**) as illustrated in Scheme 1. Due to the lability of the thioester moiety to nucleophilic displacement, the octanoic acid will be incorporated into the molecule at a later stage. Literature precedence[9] suggests that the reaction of carboxylic acid with the allylic secondary alcohol to afford the corresponding ester is achievable. We envisioned that our synthetic approach involving the esterification–macrolactamization would render the compounds impervious to β-elimination. Therefore, we proposed to prepare largazole in a convergent manner through the assembly and cyclization of linear precursor **2**. Further disconnection of **2** at the amide linkage provides two intermediates (**3** and **4**) of similar structural complexity. The intermediate **3** should be easily obtained from β-hydroxyl ester **5** which is readily accessible through the use of *N*-acetylthiazolidinethione-mediated asymmetric aldol reaction.[10] Furthermore, thiazoline–thiazole derivative **4** would be accessible by applying a similar approach developed by Pattenden and coworkers.[11]

The fragment **3** (Scheme 2) was constructed in five steps from 3-(*tert*-butyldimethylsilyloxy)-1-propanol (**9**):[12] Treatment of alcohol **9** with TEMPO-catalyzed oxidation with trichloroisocyanuric acid to provide the requisite propanal derivative,[13] which was then reacted with (carbethoxymethylene)triphenylphosphorane to afford the corresponding (*E*)-α,δ-unsaturated ester **10** in 84% yield over two steps. The conjugated ester **10** was subjected to successive reduction with DIBAL-H and oxidation with Dess–Martin periodinane to afford enal **11**. Reaction of **11** with Nagao's chiral *N*-acetylthiazolidine-2-thione[10a] under Vilarrasa's conditions[10j] proceeded in high diastereoselectivity to yield the readily separable allylic alcohol **13** and its minor diastereomer (dr = 14:1).[14] Displacement of the thiazolidinethione auxiliary with 2-(trimethylsilyl) ethanol mediated by DMAP was carried out smoothly under mild conditions to afford ester **5** in 94% yield. Finally, esterification of the allyl alcohol **5** with *N*-Fmoc-valine was promoted by DCC in the presence of catalytic quantity of DMAP produced the key intermediate **3** in 91% yield. As shown in Scheme 3, a modified Hantzsch reaction[15] was employed for the synthesis of thiazole-4-ester **15**.[16]

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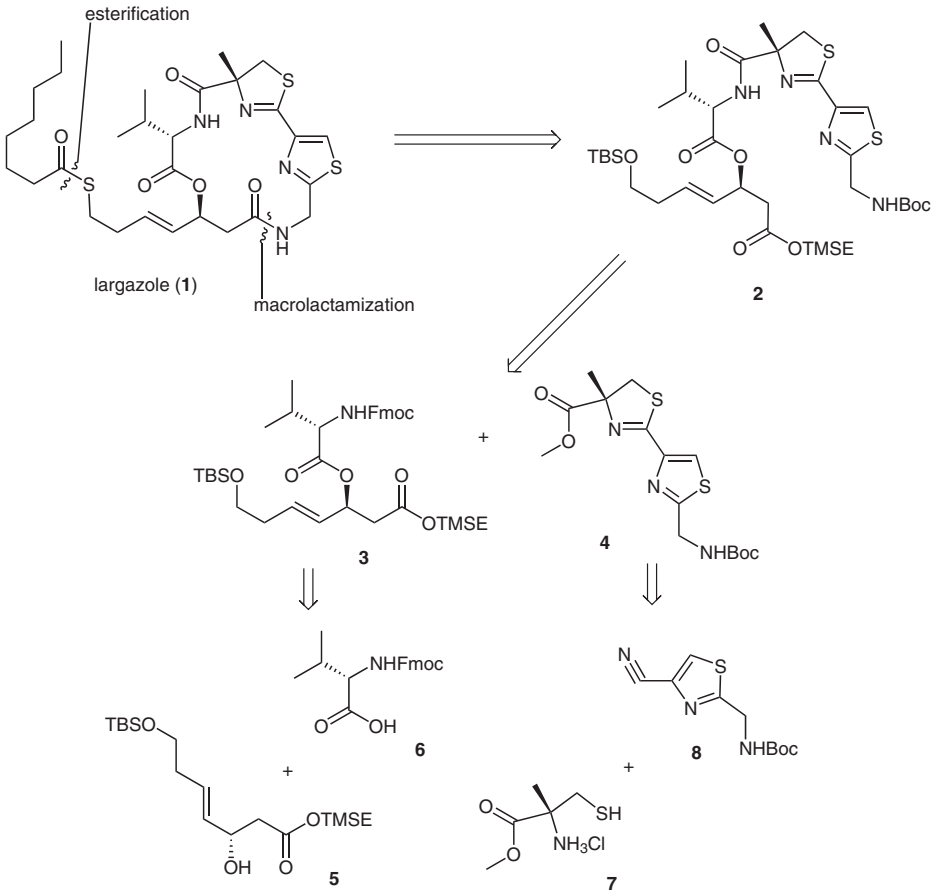
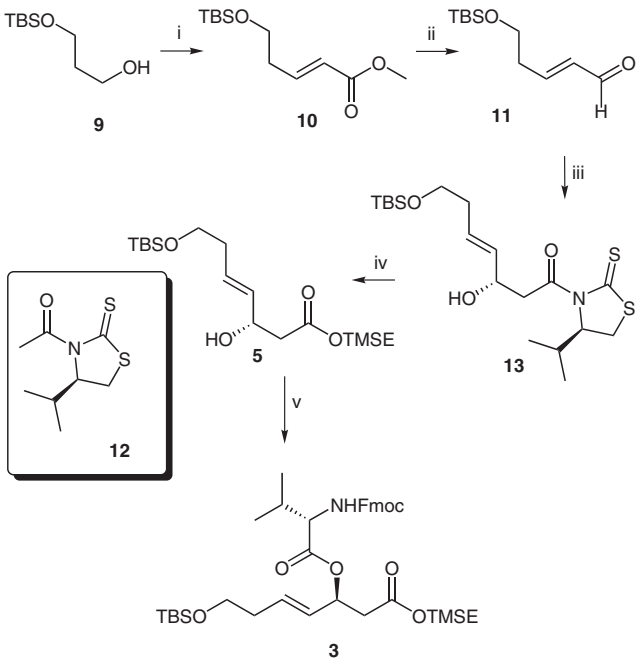
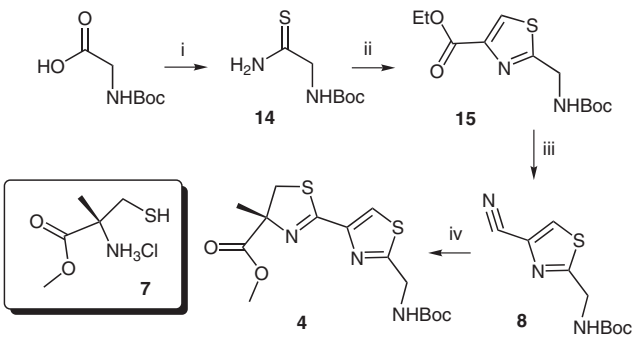


Scheme 1 Retrosynthetic analysis

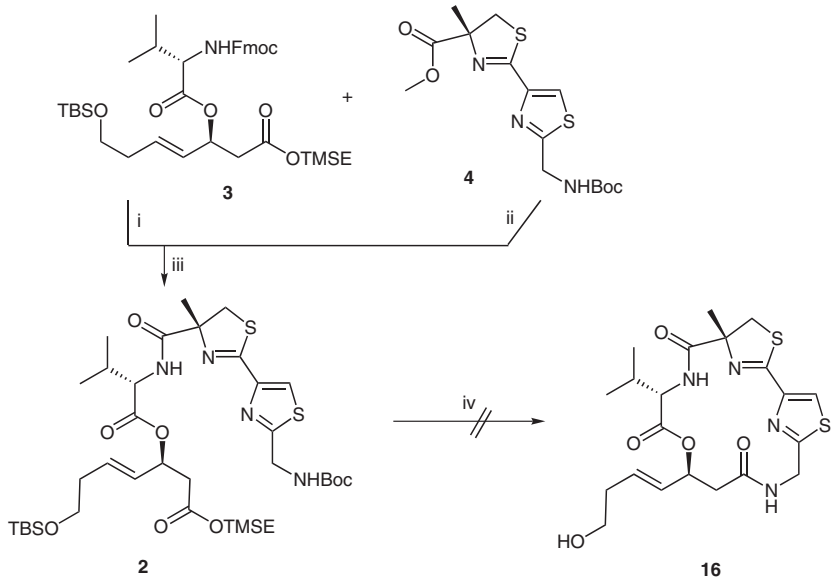


Scheme 2 Preparation of intermediate **3**. *Reagents and conditions*: (i) (a) trichloroisocyanuric acid, TEMPO, CH_2Cl_2, 91%; (b) Ph_3PCHCO_2Me, CH_2Cl_2, 92%; (ii) (a) DIBAL-H, THF, 83%; (b) DMP, CH_2Cl_2, 81%; (iii) **12**, $TiCl_4$, DIPEA, CH_2Cl_2; then **11**, –78 °C, 83% (dr = 14:1); (iv) $TMSCH_2CH_2OH$, DMAP, CH_2Cl_2, 94%; (v) L-Fmoc-Val-OH, DCC, DMAP, CH_2Cl_2, 91%.

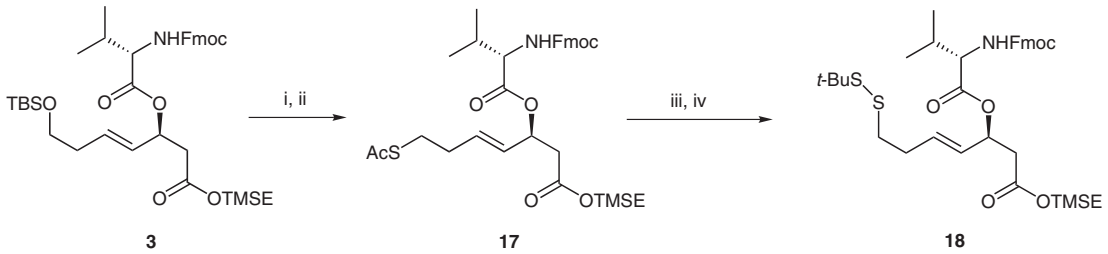


Scheme 3 Synthesis of fragment **4**. *Reagents and conditions*: (i) (a) *i*-BuOCOCl, Et_3N, THF, NH_4OH; (b) P_2S_5, Na_2CO_3, THF, 83% (over 2 steps); (ii) $KHCO_3$, –15 °C, $BrCH_2COCO_2Et$, TFAA, 2,6-lutidine, –20 °C, 91%; (iii) (a) NH_3–MeOH, MeOH, 51%; (b) $POCl_3$, pyridine, CH_2Cl_2, 63%; (iv) **7**, Et_3N, MeOH, 50 °C, 51%.

Hence the thioamide **14** prepared in 83% yield from *N*-Boc-glycine was reacted with ethyl bromopyruvate at –15 °C, followed by dehydration of the resulting hydroxylthiazoline with trifluoroacetic anhydride (TFAA) and 2,6-lutidine to afford the thiazole-4-ester **15** in 91% yield. The ester **15** was next converted to the corresponding amide and then to the nitrile **8**.[17] This then set to the stage for the cyclocondensation. Thus, condensation reaction between the nitrile **8** and the (*R*)-2-methylcysteine methyl ester hydrochloride (**7**) prepared according to Pattenden's



Scheme 4 Attempted marcrolactamization. *Reagents and conditions*: (i) *i*-Pr_2NH, CH_2Cl_2; (ii) LiOH, H_2O–THF; (iii) Mukaiyama reagent, DIPEA, CH_2Cl_2, 0 °C to r.t., 90% (two steps); (iv) (a) TFA, CH_2Cl_2; (b) various coupling reagents.

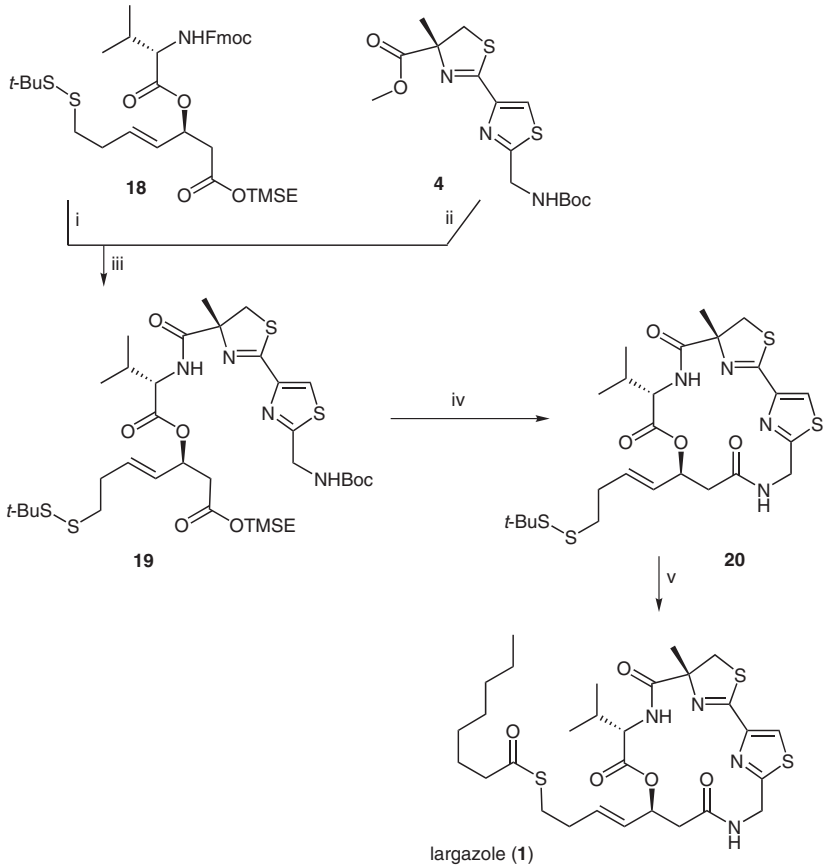


Scheme 5 Synthesis of disulfide **18**. *Reagents and conditions:* (i) HF–py, py, THF, 82%; (ii) (a) TsCl, Et_3N, DMAP, CH_2Cl_2; (b) KSAc, DMF, 83% in two steps; (iii) K_2CO_3, MeOH, 10 min, 66%; (iv) (a) DTNP, CH_2Cl_2, 2 h, (b) *t*-BuSH, Et_3N, MeOH, 10 min, 75% in two steps.

procedure[11b] led to the key intermediate **4** as viscous oil in 51% yield.

With the synthesis of the key subunits **3** and **4** completed, the assembling of the macrocycle **16** was investigated (Scheme 4). Removal of the Fmoc protecting group in **3** by the action of diisopropylamine yielded the corresponding amine, which was then condensed with the acid derived from the saponification of methyl ester in compound **4** by the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide) to furnish the linear depsipeptide **2** in excellent yield. At this juncture, global deprotection of **2** with trifluoroacetic acid followed by a marcrolactamization became our next goal. Hence, treatment of depsipeptide **2** with TFA provided the fully deprotected acyclic precursor, which was then submitted to macrolactamization. Unfortunately, all attempts at this point to effect macrocyclization that employed a variety of coupling reagents (e.g., Mukaiyama reagent, DCC, HATU, BOPCl, PYBOP) led only to the formation of uncharacterizable products. The failure of the macrolactamization was not readily explained, however, we assumed that the homoallylic alcohol might be involved in the protecting group migration or intramolecular cyclization, presumably due to its nucleophilic nature. To circumvent the problem associated with the protecting group of the homoallylic alcohol in **3**, we decided to convert **3** into the corresponding disulfide **18** (Scheme 5). Thus, removal of the TBS protective group in **3** with HF–pyridine afforded the corresponding alcohol in 82% yield. This was then subjected to tosylation followed by displacement with potassium thioacetate in DMF to give **17** in good yield. Treatment of **17** with potassium carbonate in methanol regenerated the corresponding free thiol which was then reacted successively with the thiol-specific reagent, 2,2′-dithiobis(5-nitropyridine) (DTNP)[18] and *t*-BuSH in the presence of triethylamine to afford disulfide **18** in 50% yield over three steps.

With disulfide **18** in hand, efforts were focused on the key macrocyclization again (Scheme 6). Hydrolysis of the methyl ester in **4** afforded the corresponding acid, which was coupled to the free amine resulting from the diethylamine deprotection of compound **18**, to provide the linear depsipeptide **19** in 91% yield. Deprotection of both Boc and TMSE ester with TFA smoothly delivered the acyclic precursor which was then treated with a highly effective activating reagent HATU in DMF to afford the corresponding cyclodepsipeptide **20** in 61% yield.[19] Tributylphosphine-promoted reductive cleavage of the di-



Scheme 6 Completion of the total synthesis. *Reagents and conditions*: (i) Et_2NH, MeCN; (ii) LiOH, H_2O–THF; (iii) Mukaiyama reagent, DIPEA, CH_2Cl_2, 91%, two steps from **18**; (iv) (a) TFA, CH_2Cl_2; (b) HATU, HOAT, DIPEA, DMF, 61%, two steps; (v) (a) PBu_3, THF–H_2O; (b) *n*-$C_7H_{15}COCl$, DIPEA, DMAP, CH_2Cl_2, 78%, two steps.

sulfide bond in **20** gave the corresponding thiol which was then reacted with octanoyl chloride in the presence of DMAP to afford largazole in 78% yield.[20] The optical rotation of the synthetic product, $[\alpha]_D^{20}$ 18.5 (*c* 0.2, MeOH), was in close agreement with the value reported in the literature for natural largazole, $[\alpha]_D^{20}$ 22 (*c* 0.1, MeOH). The ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) spectra for this compound exactly matched the data reported for naturally derived largazole. Thus, the original assignment of relative and absolute configuration of largazole has been corroborated via unambiguous total synthesis.

In summary, we have accomplished the total synthesis of largazole from 3-[(*tert*-butyldimethylsilyl)oxy]propanol in 5.8% overall yield with the longest linear sequence being 14 steps. This synthesis confirmed the structure of largazole and allowed for the preparation of significant quantities of the desired material for biological, conformational, and structure/conformation–activity studies. The route is highlighted by the efficient generation of the enantiomeric pure **5** employing Nagao thiazolidinethione auxiliary for a diastereoselective acetate aldol reaction. The application of this chemistry to the preparation of novel largazole analogues for biological evaluation is under way and will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Procedure for the Preparation of Intermediate 13**
(*R*)-3-Acetyl-4-isopropyl-1,3-thiazolidine-2-thione (**12**, 821 mg, 4.0 mmol) was dissolved in CH_2Cl_2 (10 mL), $TiCl_4$ (751 mg, 4.0 mol) was added at 0 °C. After 5 min, the reaction was brought to –78 °C, DIPEA (516 mg, 4.0 mmol) was added via a syringe over 10 min. The reaction was kept at –78 °C for 2 h before aldehyde **11** (428.3 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) was added dropwise. Saturated NH_4Cl (20 mL) was added to the reaction mixture and CH_2Cl_2 (3 × 30 mL) was used for extraction. The combined organic phases were dried over anhyd $MgSO_4$ and concentrated in vacuo to give the crude product, which was purified by chromatography on SiO_2, eluting with EtOAc–hexane (1:8), to afford the desired compound **13** (692.1 mg, 83%) along with the minor isomer (53.2 mg, 6%).

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(19) **Cyclodepsipeptide 20**
$[\alpha]_D^{20}$ 17.5 (*c* 0.2, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.75 (s, 1 H), 7.18 (d, 1 H, *J* = 9.3 Hz), 6.50 (dd, 1 H, *J* = 2.7, 9.0 Hz), 5.88 (dd, 1 H, *J* = 6.9, 14.6 Hz), 5.65–5.71 (m, 1 H), 5.54 (dd, 1 H, *J* = 6.7, 15.5 Hz), 5.26 (dd, 1 H, *J* = 9.4, 17.6 Hz), 4.60 (dd, 1 H, *J* = 3.6, 9.4 Hz), 4.27 (dd, 1 H, *J* = 3.1, 17.6 Hz), 4.03 (d, 1 H, *J* = 11.3 Hz), 3.28 (t, 1 H, *J* = 10.5 Hz), 2.85 (dd, 1 H, *J* = 9.9, 16.3 Hz), 2.67–2.75 (m, 3 H), 2.37–2.46 (m, 2 H), 2.06–2.14 (m, 1 H), 1.86 (s, 3 H), 1.32 (s, 9 H), 0.68 (d, 3 H, *J* = 6.9 Hz), 0.53 (d, 3 H, *J* = 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.5, 169.3, 168.8, 167.9, 164.5, 147.4, 132.8, 128.1, 124.1, 84.3, 71.9, 57.7, 47.8, 43.2, 41.0, 40.4, 39.4, 34.0, 31.8, 29.9, 24.1, 18.8, 16.6. ESI-MS: *m/z* (%) = 585.17 (100.0), 607.15 (88.8). ESI-HRMS: *m/z* calcd for $C_{25}H_{37}N_4O_4S_4$ $[M + H]^+$: 585.1698; found $[M + H]^+$: 585.1689.

(20) **Procedure for the Synthesis of Largazole (1)**
Compound **20** (9.9 mg, 0.02 mmol) was dissolved in degassed THF–H_2O (v/v = 4:1, 2 mL) and treated with *n*-Bu_3P (6.1 mg, 0.03 mmol) at r.t. for 6 h. The reaction solution was made up to 50 mL with EtOAc and dried over anhyd Na_2SO_4. The free thiol intermediate was obtained after removal of solvent in vacuo. The thiol intermediate was then dissolved in CH_2Cl_2 (5 mL), DIPEA (21.9 mg, 0.17 mmol), and octanoyl chloride (22 mg, 0.136 mmol) was added at 0 °C followed by a catalytic quantity of DMAP. The reaction mixture was stirred at r.t. for 10 min and then quenched by sat. $NaHCO_3$ (5 mL). CH_2Cl_2 (3 × 30 mL) was used for extraction. The combined organic phases were dried over anhyd Na_2SO_4 and concentrated in vacuo to give the crude product. Purification with chromatography on SiO_2, using EtOAc–hexane (2:1), provided the target molecule **1** (8.2 mg, 0.0132 mmol, 78%).
$[\alpha]_D^{20}$ 18.5 (*c* 0.2, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (s, 1 H), 7.15 (d, 1 H, *J* = 9.3 Hz), 6.46 (dd, 1 H, *J* = 2.6, 9.5 Hz), 5.80–5.84 (m, 1 H), 5.65–5.68 (m, 1 H), 5.51 (dd, 1 H, *J* = 7.1, 15.5 Hz), 5.29 (dd, 1 H, *J* = 9.4, 17.6 Hz), 4.61 (dd, 1 H, *J* = 3.3, 9.2 Hz), 4.27 (dd, 1 H, *J* = 2.8, 17.6 Hz), 4.05 (d, 1 H, *J* = 11.3Hz), 3.28 (d, 1 H, *J* = 11.3 Hz), 2.90 (t, 2 H, *J* = 7.2 Hz), 2.86 (dd, 1 H, *J* = 10.5, 16.5 Hz), 2.68 (dd, 1 H, *J* = 2.0, 16.3 Hz), 2.53 (t, 2 H, *J* = 7.4 Hz), 2.29–2.33 (m, 2 H), 2.07–2.13 (m, 1 H), 1.87 (s, 3 H), 1.62–1.66 (m, 2 H), 1.25–1.30 (m, 8 H), 0.87 (t, 3 H, *J* = 6.8 Hz), 0.69 (d, 3 H, *J* = 7.0 Hz), 0.51 (d, 3 H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.4, 173.5, 169.4, 168.9, 167.9, 164.6, 147.4, 132.7, 128.4, 124.2, 84.4, 72.1, 57.7, 44.1, 43.3, 41.1, 40.4, 34.2, 32.2, 31.6, 29.0, 28.9, 27.9, 25.6, 24.2, 22.6, 18.9, 16.6, 14.0. ESI-MS: *m/z* (%) = 623.23 (44.5) $[M + H]^+$, 645.21 (100.0) $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{29}H_{43}N_4O_5S_3$ $[M + H]^+$: 623.2396; found: 623.2371 $[M + H]^+$.