Regular Article

Synthesis and Structural Revision of Cyslabdan

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Cyslabdan was isolated from the culture broth of *Streptomyces* sp. K04-0144 as a new potentiator of imipenem activity against methicillin-resistant *Staphylococcus aureus*. We accomplished the synthesis of cyslabdan according to a previously reported structure. However, we subsequently found that this structure was incorrect; our analysis of natural cyslabdan showed that it possessed *R* stereochemistry at the C8 position, not *S*, as had previously been reported. Thus, we completed the protecting-group-free synthesis of the correct structure of cyslabdan, which is described herein.

Key words cyslabdan; structure revision; protecting-group-free synthesis; imipenem activity potentiator; methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) is known as a major nosocomial pathogen that has developed resistance to many antibiotics.[1] Moreover, MRSA has been reported to be developing resistance to the last-resort antibiotic vancomycin.[2,3] Although it is increasingly necessary to find new antimicrobial agents for the treatment of MRSA infections, it is not an easy task. Therefore, we attempted a new approach in which we screened microbial potentiators of imipenem activity against MRSA. Consequently, cyslabdan, a labdane-type diterpene containing *N*-acetyl-L-cysteine in a neopentyl-like position was isolated from the culture broth of the actinomycete strain K04-0144 and was found to be a strong potentiator of imipenem activity against MRSA[4,5] (Fig. 1). While cyslabdan exhibits almost no anti-MRSA activity by itself (minimum inhibitory concentration (MIC), 64 μg/mL), when used in conjunction with other antibiotics, it enhances their imipenem activities against MRSA over 1000-fold. This enhancement indicates that clinically resistant MRSA strains become clinically susceptible in the presence of cyslabdan. Recently, chemical biology investigations revealed that cyslabdan inhibits FemA, which is involved in the synthesis of the pentaglycine interpeptide bridge of the peptidoglycan of MRSA.[6] The biosynthetic pathway of cyslabdan was also elucidated.[7] The absolute configuration of the *N*-acetylcysteine moiety and the relative configuration of the labdane-type diterpene moiety were determined, although the absolute configuration of the latter was unclear.[4] Due to its intriguing structural features and biological profile, this natural product was selected as an attractive target for synthesis. Herein, we describe the synthesis of the reported and revised structures (**1**) and (**2**) of cyslabdan, allowing the determination of its absolute configuration.

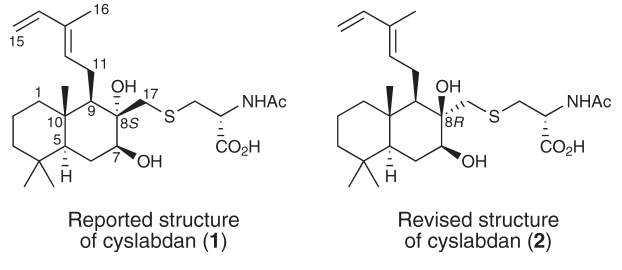

Fig. 1. Reported and Revised Structures (**1**) and (**2**) of Cyslabdan

Results and Discussion

First Approach to the Synthesis of 1: Introduction of a Cysteine Unit *via* an Epoxide Ring-Opening Reaction Initially, we hypothesized that the unknown absolute configuration of **1** would be similar to the configuration shown in Fig. 1, which is based on the absolute configuration of decaline units found in several natural labdane-type diterpenes[8] and our previous report[4] on the relative configuration. For the synthesis of the reported cyslabdan structure (**1**), the introduction of the *N*-acetyl-L-cysteine unit at the sterically hindered C17 (cyslabdan numbering), in which the neopentyl-like position is axial, was recognized as the most challenging step. To complete this step, the selection and introduction of a suitable leaving group at C17 to allow an S_N2 reaction is necessary. This also requires the protection of the sterically hindered C8-*tertiary* hydroxyl group.[9] Taking these into consideration, the initial synthetic strategy for the reported structure of cyslabdan (**1**) was designed as shown in Chart 1, in which epoxide **3** was adopted as a key intermediate. Although the protection of the sterically hindered C8-*tertiary* hydroxy group in this strategy was unnecessary, the requisite epoxide ring-opening reaction with *N*-acetyl-L-cysteine was anticipated to be difficult given that the direction of nucleophilic attack on the epoxide was very sterically hindered and fixed. However, we expected this synthetic strategy to afford a concise and short route to the reported structure of cyslabdan (**1**). The diene unit of the epoxide **3** would be constructed from diol **4**, which could be synthesized *via* the stereoselective epoxidation and configurational inversion of the C7-hydroxy group of the known allylic

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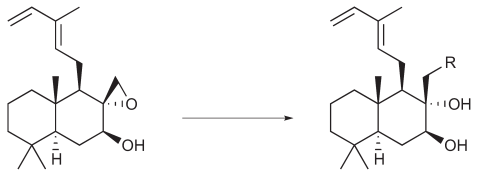
Table 1. Attempted Nucleophilic Ring-Opening of Epoxide **3** with Various Nucleophiles



3 **11**

Run	Reagents (equiv.)	Solvent(s)	Temp. (°C)	Time (h)	Result
1	*N*-Acetyl-L-cysteine *t*-butyl ester (5), *t*-BuOK (2.5)	*t*-BuOH	40	24	No reaction
2	NaSH (2)	MeOH	50	48	No reaction (R=SH)
3	NaSH (10), 15-crown-5 (12)	$(CH_2OH)_2$–DMF	50	96	No reaction (R=SH)
4	EtSH (3), NaH (3)	DMF	r.t.	16	No reaction (R=SEt)
5	KSAc (8)	DMF	50	48	No reaction (R=SAc)
6	NaI (10)	DMF	140	24	No reaction (R=I)
7	TBAI (5), $MgBr_2 \cdot Et_2O$ (2)	DMF	60	23	Decomposed
8	$HClO_4$ (5)	THF–H_2O	60	16	No reaction (R=OH)

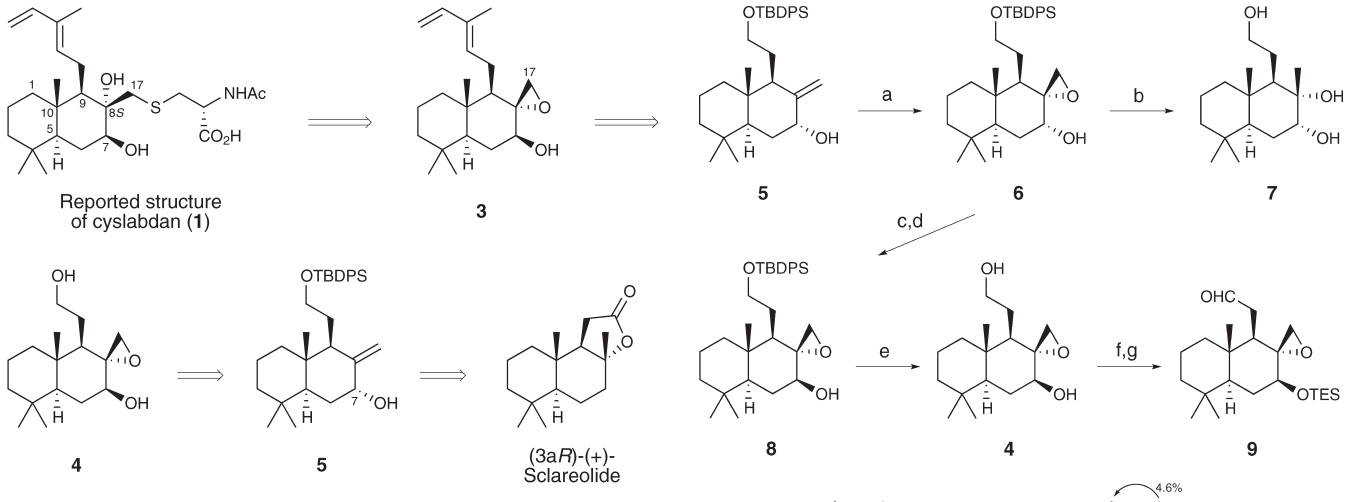
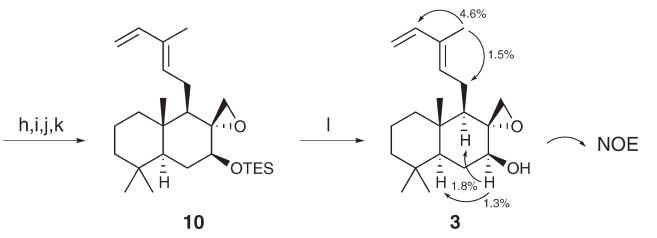


Chart 1. Retrosynthetic Analysis of **1**

alcohol **5**, which is readily prepared from commercially available (3a*R*)-(+)-sclareolide.[10]

Our synthesis commenced with the stereoselective epoxidation of the known allylic alcohol **5** with *m*-chloroperbenzoic acid (*m*CPBA) to give **6** (Chart 2). The stereochemistry of epoxide **6** was determined by the conversion of **6** to the known triol **7**[11] and the comparison of their physicochemical properties. The Mitsunobu reaction[12] of **6** led primarily to dehydration; however, configurational inversion at the C7-hydroxy group was achieved *via* Dess–Martin oxidation[13,14] and reduction with $LiAl(t\text{-}BuO)_3H$ to give **8**. Desilylation of **8** with tetrabutylammonium fluoride (TBAF) gave diol **4**, which was subjected to double protection as a bis-triethylsilyl (TES) ether followed by Swern oxidation[15] to afford aldehyde **9**. Stereoselective diene construction *via* a subsequent four-step sequence involving standard methodologies including Wittig olefination gave **10**, which was exposed to TBAF to afford the desired epoxide **3**. The stereochemistry at each chiral center in **3** was confirmed using nuclear Overhauser effect (NOE) experiments.

With the epoxide **3** in hand, the epoxide ring-opening reaction was attempted using various nucleophiles (Table 1). The

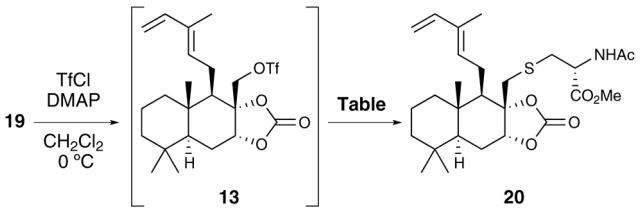


Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, 0°C, 94%; (b) LAH, Et_2O, r.t., 91%; (c) DMP, CH_2Cl_2, r.t.; (d) $LiAl(t\text{-}BuO)_3H$, Et_2O, r.t., 94% (2 steps); (e) TBAF, THF, r.t., 99%; (f) TESCl, DMAP, imidazole, DMF, 0°C, 93%; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 99%; (h) $Ph_3P{=}C(Me)CO_2Et$, benzene, 60°C, 96%; (i) DIBAL, CH_2Cl_2, −78°C; (j) MnO_2, CH_2Cl_2, r.t.; (k) Ph_3PMeBr, NaHMDS, THF, 0°C, 74% (3 steps); (l) TBAF, THF, r.t., 91%.

Chart 2. Synthesis of the Key Intermediate Epoxide **3**

treatment of **3** with *N*-acetyl-L-cysteine *t*-butyl ester in the presence of *t*-BuOK in *t*-BuOH at 40°C led to no reaction (run 1). Therefore, thiol, thiolate ions, and iodide ions were investigated as nucleophiles under harsh conditions (runs 2–6); these reactions also did not proceed. Subsequent epoxide ring-opening reactions in the presence of $MgBr_2 \cdot Et_2O$ as a Lewis acid (run 7) and under acidic conditions (run 8) were similarly unsuccessful. These results were attributed to the steric hindrance at the site of nucleophilic attack and forced us to explore an alternative synthetic route.

Table 2. S_N2 Reactions of Triflate **13** with *N*-Acetyl-L-cysteine Methyl Ester



Run	Reagents (eq.)	Solvent	Temp.	Time	Result (%)
1	*N*-Acetyl-L-cysteine methyl ester (3)	Pyridine	r.t. to 90°C	16 h	Decomposed
2	*N*-Acetyl-L-cysteine methyl ester (3), NaH (3.1)	THF	0°C to r.t.	1 h	**20** (61%)
3	*N*-Acetyl-L-cysteine methyl ester (3), NaH (2.5)	DMF	0°C	5 min	**20** (76%)

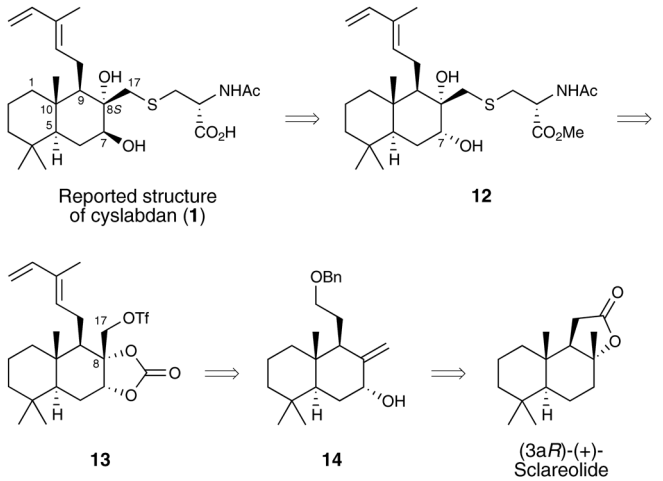
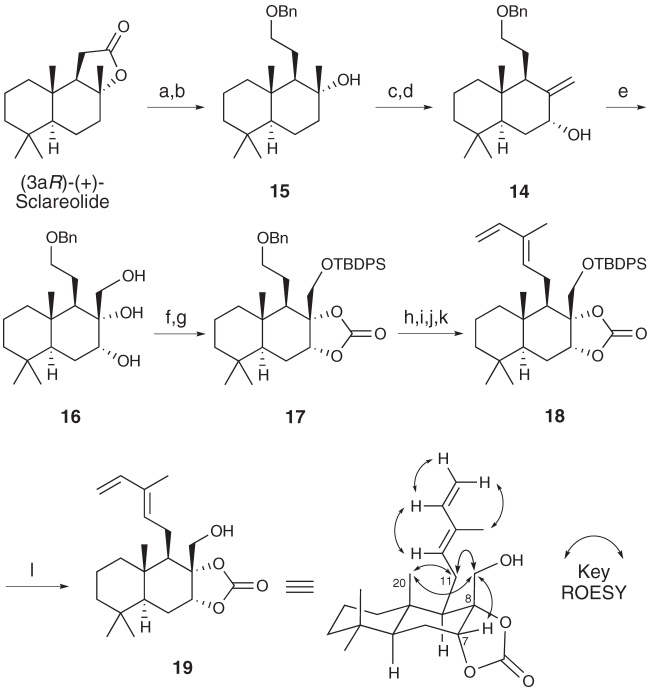


Chart 3. Second Retrosynthetic Analysis of **1**



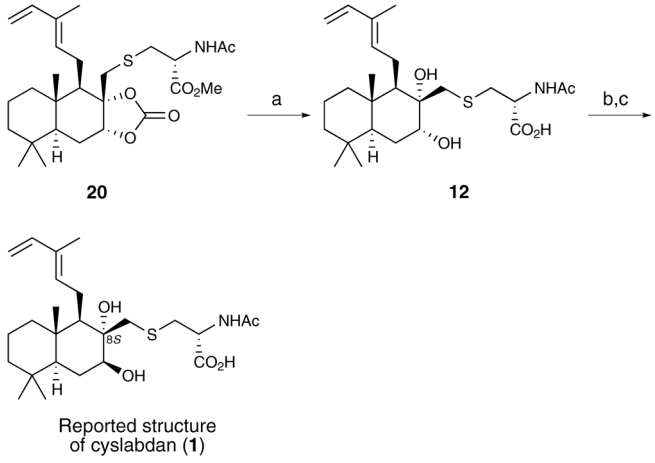
Reagents and conditions: (a) LAH, THF, 0°C; (b) BnCl, NaH, TBAI, DMF, 0°C to r.t., 93% (2 steps); (c) $SOCl_2$, DMAP, pyridine, −30°C; (d) SeO_2, TBHP, salicylic acid, CH_2Cl_2, r.t., 55% (2 steps); (e) OsO_4, NMO, THF–H_2O, r.t., 69%; (f) TBDPSCl, imidazole, DMAP, CH_2Cl_2, r.t., 95%; (g) triphosgene, pyridine, CH_2Cl_2, 0°C, 92%; (h) H_2, Pd/C, MeOH–THF, r.t.; (i) DMP, CH_2Cl_2, 0°C to r.t., 96% (2 steps); (j) $Ph_3P{=}C(Me)CHO$, toluene, reflux, 69%; (k) Ph_3PMeBr, *n*-BuLi, THF, −78 to 0°C, 87%; (l) TBAF, AcOH, THF, 0°C to r.t., 99%.

Chart 4. Synthesis of the Key Intermediate **19**

Second Approach to the Synthesis of 1: Introduction of a Cysteine Unit *via* S_N2 Reaction of a Triflate The second synthetic strategy for **1** is shown in Chart 3. The key steps in this synthesis are the S_N2 reaction of substrate **13** bearing a triflate-leaving group at the sterically hindered C17 position with an *N*-acetyl-L-cysteine methyl ester and the subsequent steric inversion of the C7-hydroxy group in the presence of a variety of other functional groups. In the S_N2 reaction, the sterically hindered C8-*tertiary* hydroxyl group in **13** must be protected. Therefore, a cyclic carbonate protecting group was selected to protect both the sterically hindered C8-*tertiary* hydroxyl group and the C7-hydroxy group. The triflate **13** including diene and C8-17 diol units was envisaged to be stereoselectively prepared from benzyl ether **14** *via* Wittig reaction and dihydroxylation. The benzyl ether **14** can be derived from commercially available (3a*R*)-(+)-sclareolide.

The benzyl ether **14** was prepared in four steps from (3a*R*)-(+)-sclareolide in a manner similar to that described for the synthesis of **5**[10] (Chart 4). The dihydroxylation of **14** with OsO_4 afforded triol **16** stereoselectively, which was then subjected to the selective protection of the primary hydroxy group as a *tert*-butyldimethylsilyl (TBDPS) ether followed by the formation of the cyclic carbonate *via* treatment with triphosgene to give **17**. Diene **18** was then constructed *via* a four-step sequence involving the deprotection of the benzyl ether, Dess–Martin oxidation, and Wittig reactions with $Ph_3P{=}C(Me)CHO$ and Ph_3PMeBr. Exposure of **18** to TBAF provided alcohol **19**. The stereochemistry of each chiral center in **19** was confirmed using rotating-frame Overhauser effect spectroscopy (ROESY) experiments.

Next, the S_N2 reaction of *N*-acetyl-L-cysteine methyl ester at the sterically hindered C17 position of triflate **13** was investigated (Table 2). Alcohol **19** was converted to the triflate **13** by treating it with trifluoromethanesulfonyl chloride, which was then subjected to the S_N2 reaction without purification due to its instability. The treatment of **13** with *N*-acetyl-L-cysteine methyl ester in pyridine at room temperature led to no reaction. When the reaction mixture was gradually warmed to 90°C, **13** decomposed without giving the desired product **20** (run 1). Subsequently, the S_N2 reaction with the sodium thiolate derivative of *N*-acetyl-L-cysteine methyl ester (prepared by pretreatment with sodium hydride) in tetrahydrofuran



Reagents and conditions: (a) $LiOH \cdot H_2O$, THF–H_2O, 0°C to r.t., 65%; (b) SO_3–pyridine, Et_3N, DMSO, r.t.; (c) $NaBH_4$, MeOH, 0°C, 31% (2 steps).

Chart 5. Completion of the Synthesis of Reported Structure **1**

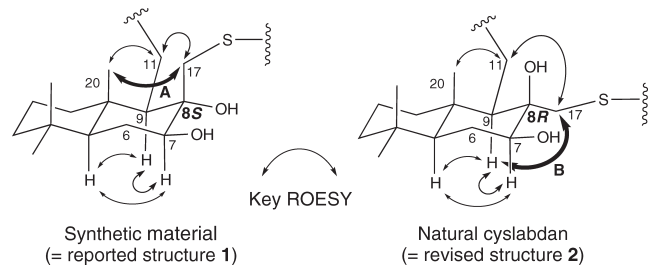


Fig. 2. ROESY Correlations Observed for the Synthetic Material and Natural Cyslabdan

(THF) succeeded in affording the desired product **20** in 61% yield (run 2). Exchanging THF with *N*,*N*-dimethylformamide (DMF) as the reaction solvent increased the yield of the desired product to 76% (run 3).

The final conversion of **20** to the reported structure of cyslabdan (**1**) was then investigated (Chart 5). Carbonate **20** was hydrolyzed under alkali conditions to give acid **12**, which was subjected to Parikh–Doering oxidation[16] followed by reduction with $NaBH_4$ to afford **1** in low overall yield.[17] Notably, although the synthesis of the reported structure of cyslabdan (**1**) was achieved, the ^{1}H-NMR spectrum of the synthetic material did not coincide with the reported data for natural cyslabdan.[4]

Therefore, natural cyslabdan was newly isolated from the culture broth of actinomycete strain K04-0144,[18] and ROESY NMR analyses of both the synthetic material (reported structure **1**) and natural cyslabdan were performed. A key cross signal **A** between the C20–CH_3 and C17–CH_2 protons that was observed for the synthetic material was not detected for the natural cyslabdan; instead, a different cross signal **B** between the C9–CH and C17–CH_2 protons was observed for the natural compound (Fig. 2). These results suggest that the stereochemistry of C8 was 8*R* not 8*S*. We carefully reviewed the reported data in 2008 to determine the absolute configuration of natural cyslabdan and understood that our previous report, in which we had determined that the stereochemistry of C8 was 8*S* despite the lack of the key cross signal **A** and the existence of the key cross signal **B**, was incorrect.

Synthesis of Cyslabdan (Revised Structure 2) and Determination of Its Absolute Configuration In light of our past research results, the synthesis of (8*R*)-cyslabdan (**2**) was attempted. The retrosynthetic analysis of **2** is shown in Chart 6. The connection of the decalin and *N*-acetyl-L-cysteine components was envisioned to occur *via* an S_N2 reaction between epoxide **21** and *N*-acetyl-L-cysteine. In contrast to the synthesis of **1**, this S_N2 reaction was expected to proceed without any difficulty. The epoxide **21** would be synthesized from lactol **22** through the formation of a diene and an epoxide. Lactol **22** could be derived from allylic alcohol **23** *via* the stereoinversion of the C7-hydroxy group and stereoselective iodolactonization. Compound **23** was expected to be prepared from commercially available (3a*R*)-(+)-sclareolide.

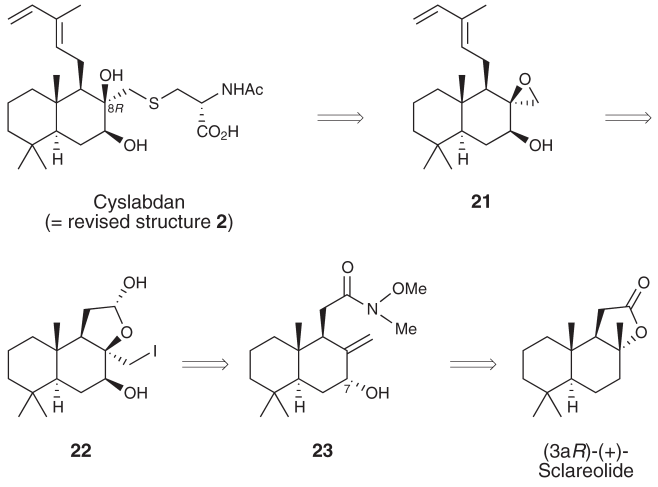
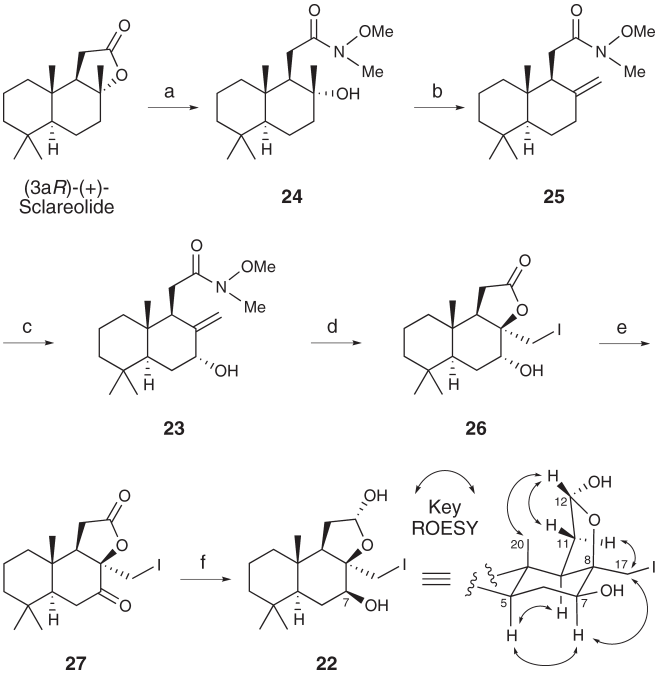
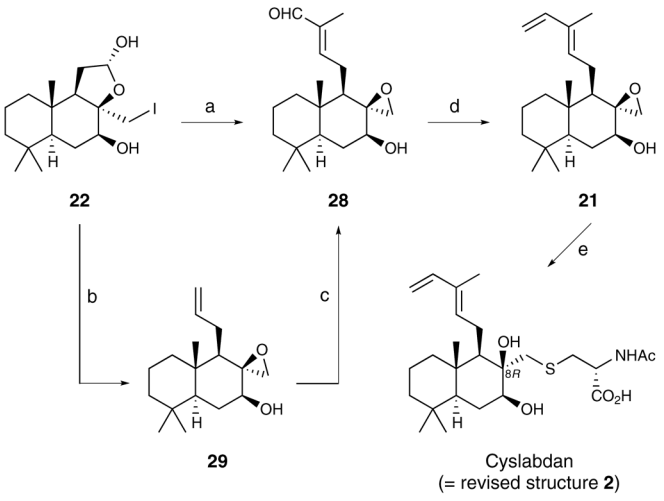


Chart 6. Retrosynthetic Analysis of **2**



Reagents and conditions: (a) MeO(Me)NH·HCl, Me_3Al, CH_2Cl_2, 0°C, 92%; (b) $SOCl_2$, pyridine, CH_2Cl_2, −78°C, 90%; (c) SeO_2, TBHP, salicylic acid, CH_2Cl_2, r.t., 61%; (d) NIS, MeCN–H_2O, r.t., 92%; (e) PCC, MS 4 Å, CH_2Cl_2, r.t., 96%; (f) DIBAL, CH_2Cl_2, −78°C, 63%.

Chart 7. Synthesis of the Key Intermediate **22**



Reagents and conditions: (a) $Ph_3P{=}C(Me)CHO$, toluene, 80°C, 17%; (b) Ph_3PMeBr, *n*-BuLi, THF, −78 to 0°C, 89%; (c) methacrolein, Grubbs second-generation catalyst, CH_2Cl_2, reflux; (d) Ph_3PMeBr, *n*-BuLi, THF, −78°C to 0°C, 74% (2 steps); (e) *N*-acetyl-L-cysteine, Na_2CO_3, MeOH–H_2O, 40°C, 87%.

Chart 8. Completion of the Synthesis of **2**

ylhydroxylamine in the presence of trimethylaluminum to afford Weinreb amide **24**[19] (Chart 7). Dehydration of **24** with thionyl chloride gave *exo*-olefin **25**,[20–31] which was subjected to allylic oxidation with SeO_2[32] to provide allylic alcohol **23**. The subsequent 5-*exo*-tet iodolactonization of **23** with *N*-iodosuccinimide (NIS) proceeded smoothly and stereoselectively to afford the desired iodolactone **26**. The pyridinium chlorochromate (PCC) oxidation of **26** provided ketone **27**, which was reduced stereoselectively with diisobutylaluminium hydride (DIBAL) to give **22** and other reduction products.[33] The stereochemistry of each chiral center in **22** was confirmed using ROESY experiments.

Next, we investigated the diene construction and the connection of the decalin unit with *N*-acetyl-L-cysteine (Chart 8). The treatment of lactol **22** with $Ph_3P{=}C(Me)CHO$ gave the desired aldehyde **28** *via* one-pot epoxide formation and stereoselective olefination; however, the yield was very low due to the generation of decomposition products. Therefore, we attempted the stepwise synthesis of **28**. The Wittig reaction of **22** with $Ph_3P{=}CH_2$ afforded olefin **29** in high yield, which was subjected to cross metathesis with methacrolein in the presence of Grubbs second-generation catalyst[34–38] to afford the desired aldehyde **28**, which was also subjected to Wittig reaction with $Ph_3P{=}CH_2$ to give epoxydiene **21**. Finally, the coupling of epoxydiene **21** with *N*-acetyl-L-cysteine under mild basic conditions afforded (8*R*)-cyslabdan (**2**). As expected, the synthetic (8*R*)-cyslabdan (**2**) was completely identical to an authentic sample of cyslabdan in all respects (^{1}H- and ^{13}C-NMR, ROESY correlations, $[\alpha]_D$, IR, MS, ultrafast liquid chromatography (UFLC), and retention time). Especially, the similarity in the optical rotations ($[\alpha]_D^{26}$=+32.4, *c*=0.1, MeOH for synthetic **2** and $[\alpha]_D^{25}$=+26.8, *c*=0.1, MeOH for natural cyslabdan[4]) established the absolute configuration of natural cyslabdan as being identical to that of **2**.

Conclusion

In summary, we have achieved the first synthesis of the reported structure of cyslabdan (**1**). The synthesis of the revised structure of cyslabdan (**2**) has been also accomplished in 16% overall yield over 10 steps without using protecting groups. These synthesized materials were used to determine the absolute configuration of natural cyslabdan (=revised structure **2**). The extension of these chemistries to the synthesis of structural analogs of **2** for structure–activity relationships is currently underway in our laboratory and will be reported in due course.

Experimental

General All reactions were conducted in flame-dried glassware under a nitrogen atmosphere employing standard techniques for the handling of air-sensitive materials. Commercial reagents were used without further purification unless otherwise indicated. Organic solvents were distilled and dried over 3 or 4 Å molecular sieves. Cold baths were prepared using ice/water (0°C) and dry ice/acetone (−78°C). Purification by flash column chromatography was performed over silica gel 60 N (spherical, neutral, particle size 40–50 μm). TLC was performed on 0.25 mm Merck silica gel 60 F254 plates and visualized using UV light (254 nm) along with phosphomolybdic acid and *p*-anisaldehyde TLC stains. Unless otherwise noted, yields are reported on chromatographically and spectroscopically pure compounds. ^{1}H-, ^{13}C-NMR spectra were recorded using an internal deuterium lock on a JNM-EX270 instrument (JEOL, Tokyo, Japan) or 400-MR, VNMRS-400, and UNITY-400 spectrometers (Agilent Technologies, Waldbronn, Germany). All NMR signals are reported in ppm relative to the internal reference standard provided by chloroform (*i.e.*, 7.26, 77.0 ppm for the ^{1}H-, ^{13}C-NMR spectra, respectively). Multiplicity data are presented as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, dd=doublet of doublets, dt=doublet of triplets, and ddd=doublet of doublet of doublets. Coupling constants (*J*) are reported in Hz. IR spectra were recorded on an FT/IR460-plus IR spectrometer (JASCO, Tokyo, Japan), and absorption data are provided in wavenumbers (cm^{-1}). Optical rotations were recorded on a DIP-1000 polarimeter (JASCO) and reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent. High-resolution (HR)-MS were obtained on a JMS-700 Mstation, JEOL JMS-AX505HA or JEOL JMS-T100LP system (JEOL) equipped with an FAB, electron ionization (EI), or electrospray ionization (ESI) HR-MS, respectively.

2-((1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)-*N*-methoxy-*N*-methylacetamide (24) A solution of MeO(Me)NH·HCl (390 mg, 3.99 mmol) in CH_2Cl_2 (2.0 mL) was treated with Me_3Al (1.06 M in *n*-hexane, 3.90 mL, 4.19 mmol) at 0°C. After stirring for 2 h at 0°C, a solution of (3a*R*)-(+)-sclareolide (500 mg, 2.00 mmol) in CH_2Cl_2 (2.0 mL) was added. After stirring for an additional 2 h at 0°C, the reaction mixture was quenched with 10% aq H_2SO_4. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (1 : 2 hexanes/EtOAc) to afford **24** (571 mg, 92%) as a colorless amorphous solid. The spectroscopic data for **24** were identical to those reported in the literature.[31]

***N*-Methoxy-*N*-methyl-2-((1*S*,4a*S*,8a*S*)-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)acetamide (25)** To a solution of **24** (10.0 g, 32.1 mmol) and pyridine (4.7 mL, 64.2 mmol) in CH_2Cl_2 (200 mL) was added dropwise a solution of $SOCl_2$ (11.7 mL, 161 mmol) and pyridine (23.3 mL,

289 mmol) in CH_2Cl_2 (90 mL) at −78°C. After stirring for 0.5 h at −78°C, the reaction mixture was quenched with a saturated aq Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (4 : 1 hexanes/EtOAc) to afford **25** (8.55 g, 90%) as a colorless amorphous solid. The spectroscopic data for **25** were identical to those reported in the literature.[31)]

2-((1*R*,3*R*,4a*S*,8a*S*)-3-Hydroxy-5,5,8a-trimethyl-2-methylenedecahydronaphthalen-1-yl)-*N*-methoxy-*N*-methylacetamide (23) A solution of **25** (5.00 g, 17.0 mmol) in CH_2Cl_2 (85 mL) was treated with SeO_2 (37.8 mg, 0.341 mmol), salicylic acid (235 mg, 1.70 mmol), and *tert*-butylhydroperoxide (TBHP) (5.0 M solution in decane, 10.2 mL, 51.1 mmol) at room temperature. After stirring for 24 h at room temperature, the reaction mixture was quenched with a saturated aq $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (1 : 1 hexanes/EtOAc) to afford **23** (3.22 g, 61%) as an amorphous brown solid: $[\alpha]_D^{26}$ −69.1 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3455, 3021, 1648, 1388, 1215, 1036; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.91 (s, 1H), 4.52 (s, 1H), 4.31 (t, 1H, J=2.8 Hz), 3.68 (s, 3H), 3.10 (s, 3H), 2.93 (dd, 1H, J=10.4, 3.6 Hz), 2.60 (dd, 1H, J=16.0, 10.4 Hz), 2.39 (dd, 1H, J=16.0, 3.6 Hz), 1.85 (dt, 1H, J=13.2, 2.8 Hz), 1.75 (dd, 1H, J=13.2, 2.8 Hz), 1.55–1.13 (m, 7H), 0.86 (s, 3H), 0.77 (s, 3H), 0.67 (s, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ: 174.4, 150.8, 109.1, 73.5, 61.4, 47.2, 46.2, 42.0, 39.1, 38.7, 33.3, 33.1, 32.5, 30.5, 26.9, 21.7, 19.3, 13.8; HR-MS (ESI) $[M+Na]^+$ Calcd for $C_{18}H_{31}NNaO_3$ 332.2202. Found 332.2203.

(3a*R*,4*R*,5a*S*,9a*S*,9b*R*)-4-Hydroxy-3a-(iodomethyl)-6,6,9a-trimethyldecahydronaphtho[2,1-*b*]furan-2(3a*H*)-one (26) To a solution of **23** (2.71 g, 8.75 mmol) in MeCN–H_2O (2 : 1, 88 mL) was added NIS (3.94 g, 17.5 mmol) at room temperature. After stirring for 1 h at room temperature, the reaction mixture was quenched with a saturated aq Na_2CO_3 solution and a saturated aq $Na_2S_2O_3$ solution. The aqueous layer was extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (4 : 1 hexanes/EtOAc) to afford **26** (3.17 g, 92%) as an amorphous yellow solid: $[\alpha]_D^{26}$ −13.5 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3488, 2851, 2067, 1771, 1418, 1214, 1060; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.34 (t, 1H, J=8.8 Hz), 3.96 (d, 1H, J=11.2 Hz), 3.27 (d, 1H, J=11.2 Hz), 2.82 (dd, 1H, J=19.2, 11.2 Hz), 2.40 (dd, 1H, J=19.2, 4.0 Hz), 2.12 (dd, 1H, J=11.2, 4.0 Hz), 1.93 (dt, 1H, J=18.4, 8.8 Hz), 1.61–0.86 (m, 8H), 0.93 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ: 176.2, 88.9, 70.1, 54.9, 48.2, 42.6, 41.6, 37.0, 33.6, 32.3, 31.1, 27.2, 21.2, 18.1, 17.0, 15.5; HR-MS (ESI) $[M+Na]^+$ Calcd for $C_{16}H_{25}NaIO_3$ 415.0746. Found 415.0741.

(3a*R*,5a*S*,9a*S*,9b*R*)-3a-(Iodomethyl)-6,6,9a-trimethyloctahydronaphtho[2,1-*b*]furan-2,4(3a*H*,5*H*)-dione (27) A suspension of **26** (600 mg, 1.70 mmol) and 4 Å molecular sieves (1.00 g) in CH_2Cl_2 (15 mL) was treated with PCC (660 mg, 3.06 mmol) at room temperature. After stirring for 1.5 h at room temperature, the resulting suspension was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (4 : 1 hexanes/EtOAc) to afford **27** (563 mg, 96%) as an amorphous yellow solid: $[\alpha]_D^{25}$ +66.1 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3020, 1773, 1639, 1215; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.50 (d, 1H, J=10.4 Hz), 3.27 (d, 1H, J=10.4 Hz), 2.82 (dd, 1H, J=18.0, 10.0 Hz), 2.61 (dd, 1H, J=18.8, 7.6 Hz), 2.50–2.41 (m, 3H), 1.77 (dd, 1H, J=12.2, 7.6 Hz), 1.64–1.01 (m, 6H), 0.91 (s, 3H), 0.88 (s, 3H), 0.77 (s, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ: 204.3, 174.0, 86.1, 54.6, 48.0, 41.3, 39.3, 36.2, 36.1, 33.1, 32.2, 30.0, 21.1, 17.8, 13.6, 10.3; HR-MS (ESI) $[M+Na]^+$ Calcd for $C_{16}H_{23}NaIO_3$ 413.0590. Found 413.0600.

(2*R*,3a*R*,4*S*,5a*S*,9a*S*,9b*R*)-3a-(Iodomethyl)-6,6,9a-trimethyldodecahydronaphtho[2,1-*b*]furan-2,4-diol (22) A solution of **27** (50.6 mg, 0.130 mmol) in CH_2Cl_2 (1.3 mL) was treated with DIBAL (1.02 M in *n*-hexane, 458 μL, 0.467 mmol) at −78°C. After stirring for 0.5 h at −78°C, the reaction mixture was quenched with MeOH. The organic layer was washed sequentially with 1 M HCl and H_2O, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (4 : 1 hexanes/EtOAc) to afford **22** (32.1 mg, 63%) as a colorless amorphous solid: $[\alpha]_D^{25}$ −27.0 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3486, 2932, 1423, 1215, 1061; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.50 (t, 1H, J=6.0 Hz), 4.06 (dd, 1H, J=11.6, 6.4 Hz), 3.70 (d, 1H, J=10.4 Hz), 3.62 (d, 1H, J=10.4 Hz), 2.28 (d, 1H, J=7.6 Hz), 2.22 (dd, 1H, J=14.2, 6.0 Hz), 1.99 (ddd, 1H, J=14.2, 7.6, 6.0 Hz), 1.81 (ddd, 1H, J=11.6, 6.4, 0.8 Hz), 1.57–0.80 (m, 8H), 0.91 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ: 99.1, 85.9, 71.4, 56.5, 49.5, 41.4, 40.8, 35.8, 35.3, 33.6, 32.8, 27.8, 22.3, 18.1, 15.7, 12.9; HR-MS (ESI) $[M+Na]^+$ Calcd for $C_{16}H_{27}NaIO_3$ 417.0903. Found 417.0904.

(1*R*,2*S*,3*S*,4a*S*,8a*S*)-1-Allyl-5,5,8a-trimethyloctahydro-1*H*-spiro[naphthalene-2,2′-oxiran]-3-ol (29) To a suspension of Ph_3PMeBr (214 mg, 0.600 mmol) in THF (0.6 mL) was added dropwise *n*-BuLi (1.63 M in THF, 367 μL, 0.600 mmol) at −78°C. After stirring for 1 h at 0°C, a solution of **22** (33.7 mg, 0.0855 mmol) in THF (0.5 mL) was added. After stirring for an additional 1 h at 0°C, the reaction mixture was quenched with a saturated aq NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (12 : 1 hexanes/EtOAc) to afford **29** (20.0 mg, 89%) as a colorless amorphous solid: $[\alpha]_D^{25}$ +36.3 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3476, 3078, 2958, 2928, 1521, 1398, 1215, 1082; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.70 (m, 1H), 4.97–4.92 (m, 2H), 3.66 (dt, 1H, J=11.6, 5.2 Hz), 2.87 (d, 1H, J=4.8 Hz), 2.62 (d, 1H, J=4.8 Hz), 2.05–2.00 (m, 2H), 1.92 (brd, 1H, J=11.6 Hz), 1.77–1.63 (m, 2H), 1.62–0.90 (m, 8H), 0.90 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ: 140.1, 114.7, 69.3, 60.0, 52.4, 50.4, 44.9, 41.9, 39.4, 39.0, 33.4, 33.3, 30.6, 25.5, 21.6, 18.5, 14.6; HR-MS (ESI) $[M+Na]^+$ Calcd for $C_{17}H_{28}NaO_2$ 287.1987. Found 287.1973.

(1*R*,2*S*,3*S*,4a*S*,8a*S*)-5,5,8a-Trimethyl-1-((*Z*)-3-methylpenta-2,4-dien-1-yl)octahydro-1*H*-spiro[naphthalene-2,2′-oxiran]-3-ol (21) A solution of **29** (29.6 mg, 0.112 mmol) in CH_2Cl_2 (2.2 mL) was treated with methacrolein (173 μL, 1.68 mmol) and a catalytic amount of Grubbs second-generation catalyst (9.5 mg, 0.0112 mmol) at room temperature. After stirring for 4.5 h at reflux, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue

was semi-purified by flash silica gel column chromatography (3 : 1 hexanes/EtOAc) to afford crude **28**. To a suspension of Ph_3PMeBr (140 mg, 0.392 mmol) in THF (0.6 mL) was added dropwise *n*-BuLi (1.60 M in THF, 245 μL, 0.392 mmol) at −78°C. After stirring for 1 h at 0°C, a solution of crude **28** in THF (0.5 mL) was added. After stirring for an additional 1 h at 0°C, the reaction mixture was quenched with a saturated aq NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (12 : 1 hexanes/EtOAc) to afford **21** (20.0 mg, 2 steps, 74%) as a colorless amorphous solid: $[\alpha]_D^{25}$ +38.9 (c=1.0, $CHCl_3$); IR (neat) cm^{-1}: 3553, 3020, 2931, 2870, 1638, 1213, 1077; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.29 (dd, 1H, 17.6, 10.8 Hz), 5.28 (t, 1H, J=6.2 Hz), 5.06 (d, 1H, J=17.6 Hz), 4.91 (d, 1H, J=10.8 Hz), 3.67 (dt, 1H, J=11.6, 5.2 Hz), 2.87 (d, 1H, J=4.4 Hz), 2.47 (d, 1H, J=4.4 Hz), 2.06 (m, 2H), 1.85 (d, 1H, J=1.2 Hz), 1.85–1.77 (m, 2H), 1.71 (s, 3H), 1.64–0.82 (m, 8H), 0.91 (s, 3H), 0.88 (s, 3H), 0.85 (s, 3H); ^{13}C-NMR (400 MHz, $CDCl_3$) δ: 141.1, 134.6, 133.8, 110.7, 69.3, 60.0, 52.3, 52.2, 44.8, 41.8, 39.3, 39.2, 33.4, 33.3, 30.5, 21.6, 20.6, 18.5, 14.7, 12.0; HR-MS (ESI) $[M+Na]^+$ Calcd for $C_{20}H_{32}NaO_2$ 327.2300. Found 327.2298.

Revised Structure of Cyslabdan (2) A solution of **21** (269 mg, 0.870 mmol) in MeOH–H_2O (1 : 1, 35 mL) was treated with *N*-acetyl-L-cysteine (710 mg, 4.35 mmol) and Na_2CO_3 (1.38 mg, 13.0 mmol) at room temperature. After stirring for 15 h at 40°C, the reaction mixture was quenched with 2 M HCl and extracted with EtOAc. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash silica gel column chromatography (10 : 1 CH_2Cl_2/MeOH) to afford **2** (353 mg, 87%) as a colorless amorphous solid: $[\alpha]_D^{26}$ +32.4 (c=0.1, MeOH), (lit.[4]) $[\alpha]_D^{25}$ +26.8 (c=0.1, MeOH); IR (neat) cm^{-1}: 3490, 2949, 2834, 1654, 1411, 1201, 1019; ^{1}H-NMR (400 MHz, CD_3OD) δ: 6.34 (dd, 1H, J=17.6, 10.8 Hz), 5.52 (t, 1H, J=6.8 Hz), 5.04 (d, 1H, J=17.6 Hz), 4.86 (d, 1H, J=10.8 Hz), 4.47 (dd, 1H, J=7.6, 4.8 Hz), 3.76 (dd, 1H, J=11.2, 4.8 Hz), 3.03 (dd, 1H, J=13.2, 4.8 Hz), 2.82 (dd, 1H, J=13.2, 7.6 Hz), 2.78 (d, 1H, J=12.4 Hz), 2.62 (d, 1H, J=12.4 Hz), 2.42 (dt, 1H, J=17.6, 6.8 Hz), 2.11 (dd, 1H, J=17.6, 3.6 Hz), 1.98 (s, 3H), 1.75 (br s, 3H), 1.73–0.84 (m, 10H), 1.00 (s, 3H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C-NMR (400 MHz, CD_3OD) δ: 176.0, 173.1, 143.0, 137.5, 133.4, 110.2, 78.7, 72.8, 55.2, 54.7, 53.8, 43.0, 41.0, 39.8, 39.1, 37.3, 34.1, 34.0, 27.9, 24.3, 22.6, 22.3, 19.3, 15.9, 12.0; HR-MS (ESI) $[M+Na]^+$ Calcd for $C_{25}H_{41}NNaO_5$ 490.2603. Found 490.2600.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

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