Enantioselective Synthesis of *ent*-Stellettamide A: Asymmetric Dipolar Cycloadditions with Me_3SiCHN_2

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Dedicated to Prof. Dr. *Albert Eschenmoser* on the occasion of his 75th birthday

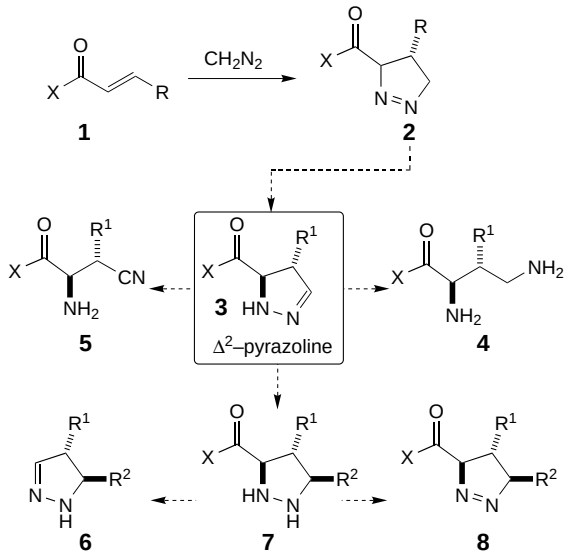
We report an enantioselective synthesis of *ent*-stellettamide A. Efficient entry into the indolizidine is possible through the application of a diastereoselective dipolar cycloaddition reaction of Me_3SiCHN_2.

Introduction and Background. – Dipolar cycloadditions are a powerful and important class of synthetic reactions for the construction of diversely functionalized five-membered heterocycles [1]. The use of nitrile oxides, azomethine ylides, carbonyl ylides, nitrones, and nitronates as the 4π-dipole component has been extensively investigated and has resulted in elegant applications to natural-products syntheses [2–4]. By contrast, the use of diazoalkanes as dipoles has not been extensively examined. The paucity of such studies may be a consequence of the fact that, with the exception of Me_3SiCHN_2, diazoalkanes are not commercially available, once prepared they are not amenable to prolonged storage, and they can be thermally unstable [5]. The adducts isolated from the dipolar additions of diazoalkanes with chiral α,β-unsaturated carboxylic-acid derivatives could serve as useful building blocks for the synthesis of optically active materials, such as diamines **4**, amino nitriles **5**, and pyrazolines **6** (*Scheme 1*) [6]. Moreover, the preparation of the simplest Δ^2-pyrazoline **3** derived from the addition of the parent diazomethane would provide access to 4-substituted tetrahydropyrazoles **7** and the corresponding 4,5-dihydro-3*H*-pyrazole **8**, formally the adducts of substituted diazomethanes with a chiral α,β-unsaturated carboxylic-acid derivative. A necessary prerequisite for the synthetic transformations outlined above, however, is that the Δ^1-pyrazoline first formed in the cycloadditions be amenable to isomerization in a controlled manner to give Δ^2-pyrazoline **3**.

The recent availability of Me_3SiCHN_2 as an inexpensive, safe diazomethane equivalent allows consideration to be given to its use as a 1,3-dipole in asymmetric dipolar cycloaddition reactions. Indeed, Me_3SiCHN_2 has been used in [3+2]-dipolar cycloadditions with unsaturated esters and nitriles; the cycloadducts isolated were subjected to nitrogen extrusion or aromatization reactions to provide cyclopropanes and pyrazoles, respectively [7][8][1]). In a singular study on the addition of Me_3SiCHN_2 with γ-substituted α,β-unsaturated esters, it had been

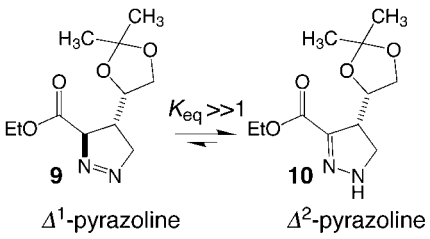
[1]) The cycloaddition of vinyl boronates and ethyl diazoacetate has been shown to give the corresponding non-conjugated Δ^2-pyrazoline following hydrolysis of the boronate adduct [8].

Scheme 1



concluded that the initially formed Δ^1-pyrazoline **9** isomerized to the Δ^2-regioisomer **10** (*Scheme 2*), thereby resulting in loss of one of the newly installed stereogenic centers [5a,b].

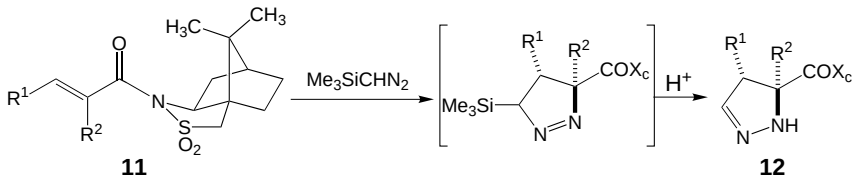
Scheme 2



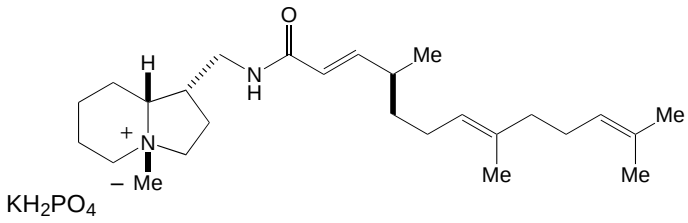
Within the context of our interest in developing reaction methods for the synthesis of amines [9] in recent work from our laboratories, we have documented that Me_3SiCHN_2 participates in asymmetric dipolar cycloaddition reactions to give optically active Δ^1-pyrazolines (*Scheme 3*) [10]. By a Si-directed protodesilylation reaction, enantiomerically enriched Δ^2-pyrazolines **12** may be isolated in good yields with excellent diastereoselectivity. The preliminary studies examined the synthetic transformations available to these heterocycles as proline surrogates, as the ability of **12** to undergo chemoselective C=N reduction and peptide-bond formation would allow these to be incorporated in peptide structures.

We subsequently chose the stellettamide A (**13**) synthesis project as a program within which to examine the versatility of asymmetric dipolar cycloaddition of

Scheme 3



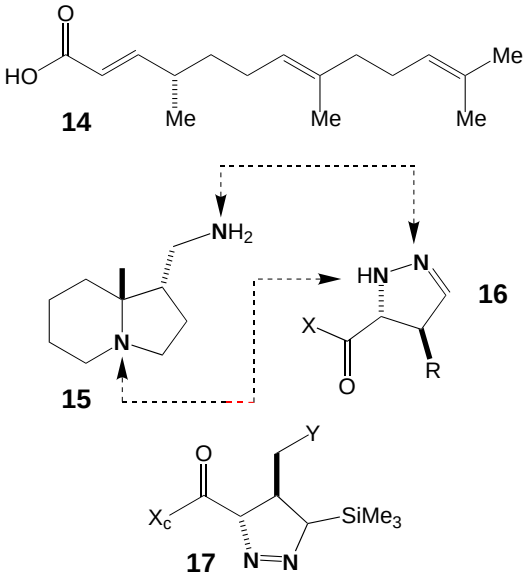
Me_3SiCHN_2 with chiral enoates [11][2]). Stellettamide A (**13**) has been recently isolated by a bioassay-guided strategy [12]. This marine metabolite possesses antifungal activity and displays cytotoxicity against K562 epithelium cell lines. Its structure was established by extensive NMR-spectroscopic experiments, allowing the relative configuration of the perhydroindolizine core to be unambiguously assigned. However, these studies provided the assignment of neither the stereogenic center present in the trienoic acid side chain nor the absolute configuration of stellettamide A (**13**). Analysis of the bicyclic core reveals a 1,3-diamine relationship whose synthesis may be amenable to the application of an asymmetric [3 + 2] diazomethane dipolar-cycloaddition reaction in which the two N-atoms of the dipole are ultimately recruited for the perhydroindolizine core.



Stelletamide A (**13**)

Results and Discussion. – The retrosynthetic disconnections that formed the basis of our plan for the preparation of stellettamide A (**13**) are illustrated below. Removal of the acyl side chain provided two fragments, trienoic acid **14** and the perhydroindolizine core **15**. The attachment of the acid side chain as a late step in the synthesis would allow both enantiomeric side chains to be prepared independently and appended to the perhydroindolizine core for comparison to natural stellettamide A. In light of the lack of information at the start of these investigations on the absolute-configurational assignment of the natural product, preparation of diastereoisomeric structures epimeric at the C(4) side chain would allow this ambiguity to be resolved. We envisioned that the perhydroindolizine core would be constructed from the asymmetric dipolar cycloaddition reaction of CH_2N_2 (or its equivalent) and a chiral enoate. In particular, the use of Me_2SiCHN_2 as the 4π component in the cycloaddition reaction could be advantageous in two regards: its commercial availability, and the use of the silyl group to control the isomerization of the initially formed Δ^1-pyrazoline **17**. Additionally, the

[2]) A preliminary account of this work in the form of a communication has been previously reported [11].



pyrazoline **16** intermediate could function as a masked form of the diamine found in the perhydroindolizine until a late stage in the synthesis.

The synthetic sequence commenced with dipolarophiles **18** and **19**, which were synthesized from the commercially available (*S*)-camphorsultam [13] and 5-hydroxy-pent-2-enoic acid [14] according to procedures analogous to those previously reported (*Scheme 4*). The dipolar cycloaddition reactions were conducted by treatment of solutions of **18** or **19** with powdered 4-Å molecular sieves, and the commercially available solution of 2.0M Me_3SiCHN_2 in hexane. The diastereoselectivity of the reaction could be optimized by varying the solvent employed in the cycloaddition step (*Table*). For the $^{i}Pr_3Si$-protected dipolarophile **18**, optimal selectivities were observed when the reaction was conducted in hexane as solvent. For the Bn-protected dipolarophile **19**, which was ultimately used as starting material for the synthesis, its insolubility in hexane presented a limitation, as the cycloaddition reaction proceeded at a rate that was not preparatively useful. This necessitated the addition of 20% CH_2Cl_2 as co-solvent to ensure dissolution of **19**. Under optimal conditions, the dipolar cycloaddition reaction of **19** with Me_3SiCHN_2 afforded the cycloadducts **20**/**21** cleanly in quantitative yields, as determined by ^{1}H-NMR spectroscopy. The workup procedure for these reactions is noteworthy, since it proved remarkably simple: the product was isolated upon removal of the molecular sieves by filtration, followed by evaporation of solvent and remaining excess Me_3SiCHN_2. Analysis of the product isolated in this manner allowed the reaction diastereoselectivity to be assayed by ^{1}H-NMR spectroscopy. Integration of the resonances at 5.58 and 5.43 ppm indicated a diastereoisomer ratio of 93:7 for the cyloadducts. At this stage, however, we were unable to unambiguously establish the nature of the diastereoisomeric products formed; in this regard, we were unable to differentiate a mixture of C(3)/C(4) *anti*-diastereoisomers *vs.* α- or β-trimethylsilanes. This issue was ultimately settled by subsequent desilylation/

isomerization (AgOTf, EtO_2CCl, Et_3N) to afford **22** in 71% yield and **23** in 6% yield (**23**/**22** 92 : 8). This diastereoisomer ratio corresponds to that which had been observed for initially formed cycloadducts **18** and **19** (93 : 7), suggesting high diasteroselectivity in the cycloaddition reaction (**19** → **20** + **21**; *Scheme 4*).

Scheme 4

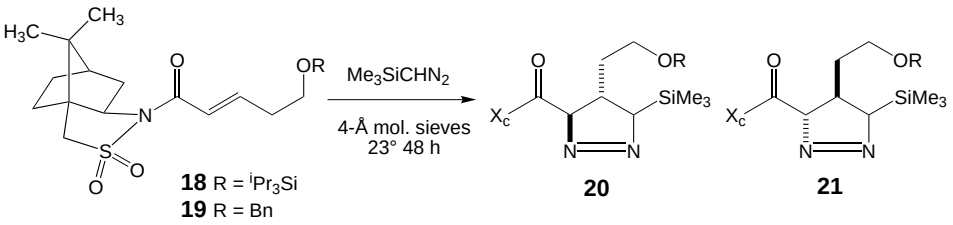


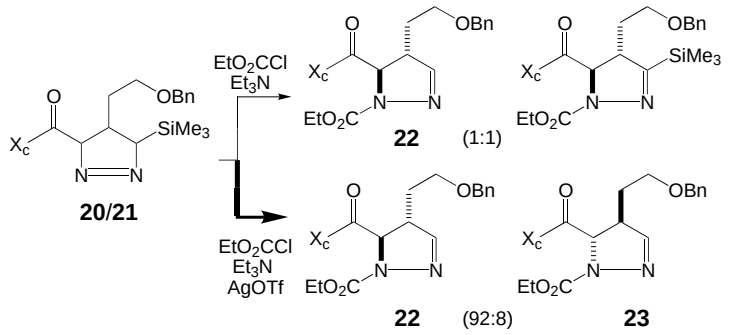
Table. *Cycloaddition Reactions of* **18** *and* **19** (*Scheme 4*)

R	Solvent	**17**/**18**
$^iPr_3Si$	CH_2Cl_2	75 : 25
	MeCN	76 : 24
	PhH	83 : 17
	THF	84 : 16
	Hexane	86 : 14
Bn	CH_2Cl_2	84 : 16
Bn	Hexane/CH_2Cl_2 4 : 1	93 : 7

The desilylative *N*-protection of **20**/**21** in high yields required some experimentation. Treatment of **20**/**21** with $(Boc)_2O$ (Et_3N, CH_2Cl_2, 23°, 4-(dimethylamino)pyridine (DMAP) regenerated starting material. When **20**/**21** was allowed to react with ethyl chloroformate (CH_2Cl_2, 0°) in the presence of amine bases, a 1 : 1 mixture of silylated and desilylated products were observed (*Scheme 5*). By contrast, a reaction mixture consisting of **22**, ethyl chloroformate, and AgOTf (CH_2Cl_2, 0°) exclusively afforded product **22** in 76% yield.

The dipolar cycloaddition of Me_3SiCHN_2 with **19** establishes the two key stereogenic centers that constitute the perhydroindolizine core of stellettamide A

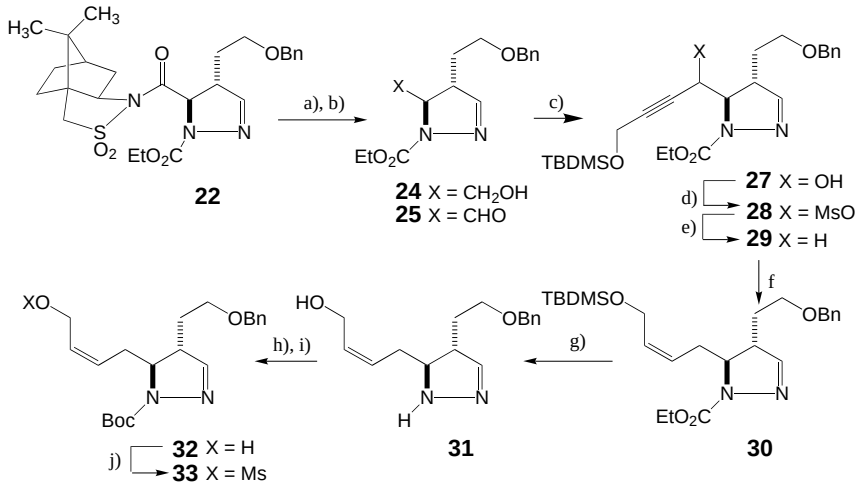
Scheme 5



(**13**). In a broader sense, the success of the desilylative isomerization from the Δ^1-pyrazoline to the Δ^2-pyrazolidine in a regio-controlled fashion opens new possibilities for the elaboration reaction of such optically active pyrazolines. Within the context of the stellettamide project, subsequent elaboration of this adduct led to the preparation of the perhydroindolizine core (*Scheme 6*). The sultam auxiliary was removed upon treatment of **22** with $LiAlH_4$, giving the corresponding primary alcohol **24** in 91% yield, which was subjected to *Swern* oxidation to afford aldehyde **25** (93%). Reaction of **25** with acetylide **26** gave secondary propargyl alcohol **27** as a 2:1 mixture of diastereoisomeric alcohols, which, without purification, was allowed to react with MsCl (Et_3N, CH_2Cl_2) to provide propargyl methanesulfonate **28** (68%, two steps). Hydrogenolysis of **28** was conducted according to a procedure reported by *Tsuji* and coworkers [15] with ammonium formate, [$Pd_2(dba)_3$], and Bu_3P to afford a mixture of desired alkyne **29** and allene products (12:1). Semihydrogenation of **29** gave (*Z*)-alkene **30** (95%). Deprotection of the primary silyl ether and the ethyl carbamate was accomplished concomitantly upon treatment of **30** with aqueous $Ba(OH)_2$ in dioxane. It is interesting to note that this reaction proved sensitive to solvent. Thus, in MeOH under otherwise identical conditions, we observed a complex mixture of products from which it was difficult to isolate **31** in pure form. Pyrazoline **31** was selectively protected[3]) (aq. NaOH, THF) with $(Boc)_2O$ to afford **32**, which was, in turn, treated with MsCl to give **33**.

The deprotection of *N*-Boc-pyrazoline and cyclization to **35** required some optimization before it was possible to effect successfully (*Scheme 7*). For example,

Scheme 6

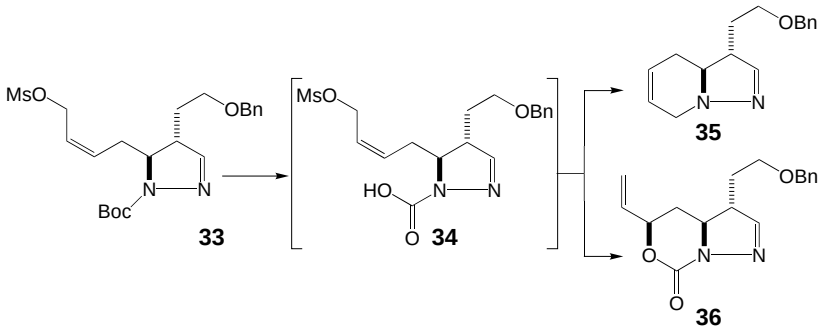


a) $LiAlH_4$, THF, −78°; 91%. b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; 93%. c) $Me_2{}^tBuSiOCH_2C{\equiv}CMgBr$ (**26**), THF, 0°. d) MsCl, Et_3N, CH_2Cl_2, 0°; 68% two steps. e) Bu_3P, [$Pd_2(dba)_3$], HCO_2NH_4, PhH; 76%. f) 5% Pd/$BaSO_4$, H_2, quinoline, MeOH, 23°, 95%. g) $Ba(OH)_2$, H_2O, dioxane, 100°. h) $(Boc)_2O$, aq. NaOH, THF, 23°; 80% two steps. i) MsCl, Et_3N, CH_2Cl_2, O°. TBDMS = (*t*-Bu)MeSi.

[3]) Interestingly, protection of the hydrazone as described was superior to other methods involving Boc_2O with Et_3N (21% yield), or Boc–ON/pyridine (20% yield).

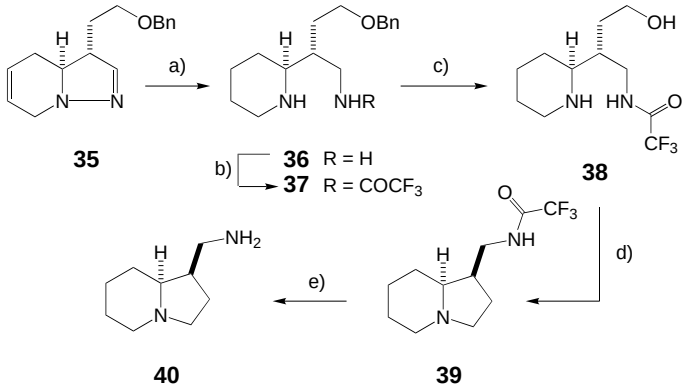
treatment of **33** with 2M HCl in dioxane did not provide any desired product **35**. Treatment with CF_3COOH (CH_2Cl_2) gave some of desired **35** along with 10–20% of **36**. The isolation of **37** is consistent with a mechanism by which the carbamic acid **34**, generated following loss of the *t*-Bu group, undergoes reaction with the allylic methanesulfonate faster than it undergoes decarboxylation. In this regard, we reasoned that, under more acidic conditions, the decarboxylation reaction might be accelerated, precluding the formation of **36**. To this end, treatment of **33** with 10% conc. H_2SO_4 in dioxane [16][4]) followed by transfer of the reaction mixture to a solution of NaOH resulted in rapid decarboxylation and formation of **35** in 83% yield.

Scheme 7



Treatment of **35** with *Ra*-Ni/H_2 effected concomitant C=C and C=N reduction along with N–N bond cleavage to give a diamine **36** (*Scheme 8*). Selective protection of the primary amine in **36** as the corresponding trifluoroacetamide yielded **37** (85% yield, two steps). Hydrogenolytic removal of the Bn group and treatment of the resulting primary alcohol **38** with CBr_4 and Ph_3P effected ring closure to give **39** in 75%

Scheme 8



a) *Ra*–Ni/H_2, EtOH, 23°. b) CF_3CO_2Et, THF, 0°; 85% two steps. c) $Pd(OH)_2$/C, HCO_2NH_4, MeOH, reflux; 85%. d) CBr_4, PPh_3, Et_3N, MeCN, 0°; 75%. e) 5% K_2CO_3, MeOH, H_2O, 23°.

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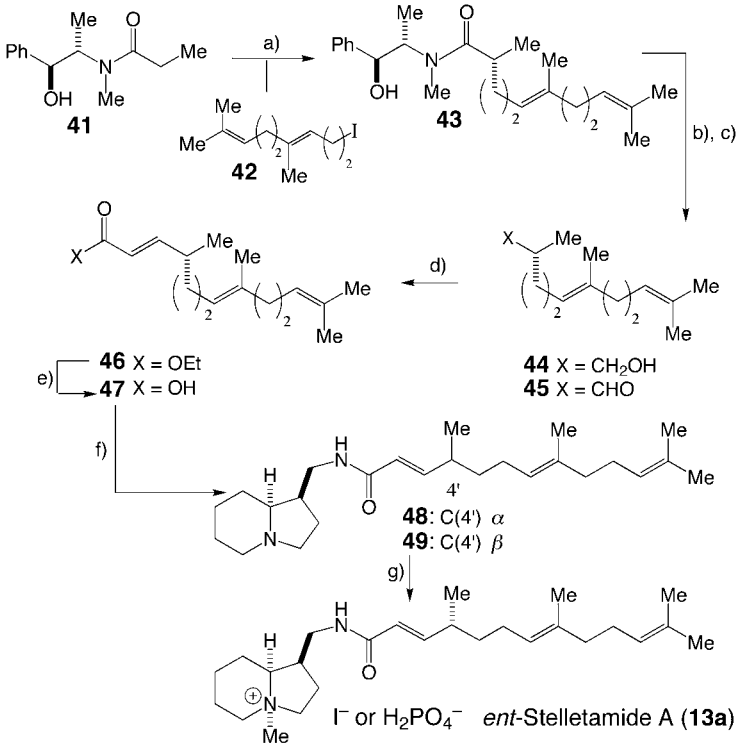
[4]) These conditions have been previously employed in the removal of *N*-Boc protecting group [11].

yield [17][5]). Following alkaline hydrolysis of the *N*-trifluoroacetamide, the perhydroindolizine core **40** of stellettamide A (**13**) was isolated.

Because the relative configuration of the trienoic acid side chain of stellettamide A (**13**) was not determined in the original isolation and characterization studies, both enantiomeric (*R*)- and (*S*)-γ-Me-substituted 2,7,11-trienoic acids were prepared (*Scheme 9*). The synthesis of each of these was possible in an expeditious manner by the recently described asymmetric alkylation methodology of *Myers et al.* [18]. We illustrate in *Scheme 9* the synthetic sequence utilized for the preparation of the (*R*)-4′-Me-substituted side chain, which was subsequently determined to correspond to the relative configuration for stellettamide A (**13**). Alkylation of **41** with **42** afforded **43** in 92% yield as a single diastereoisomer, as determined by ^{1}H-NMR spectroscopy[6]). Reductive removal of the amide auxiliary with $NH_3 \cdot BH_3$ (LDA, THF, 0°) [19] provided the primary alcohol **44** (91%), which was subsequently oxidized to aldehyde

Scheme 9



a) LiN^iPr_2, LiCl, THF; 92%. b) LiN^iPr_2, $BH_3 \cdot NH_3$, THF, 0°; 91%. c) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N. d) Ph_3PCHCO_2Et; 79%, two steps. e) Aq. LiOH, THF, reflux; 92%. f) **39**, DCC, DMAP, CH_2Cl_2; 72%. g) MeI, $KHCO_3$, MeOH; 95%.

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5) The use of CCl_4/Ph_3P in a similar cyclization reaction has been documented [12].

6) The stereoisomer purity of the alkylation product was established by reductive removal of the auxiliary to give the corresponding primary alcohol, which was converted to the derived (−)-(*R*)-3,3,3-trifluoro-2-methoxy-2-phenylacetates and analyzed by ^{1}H-NMR spectroscopy.

45. Condensation of **45** with [(ethoxycarbonyl)methylidene]triphenylphosphorane afforded **46** in 79% yield, a single diastereoisomer as determined by ^{1}H-NMR spectroscopy. Saponification (LiOH, THF, reflux) of **46** yielded trienoic acid **47**. The two enantiomeric trienoic acids **47** and *ent*-**47** were coupled with amine **40** *via* amide-bond formation (DCC, DMAP, CH_2Cl_2; 72%) to produce stellettamides diastereoisomeric at C(4′) of the trienoic-acid side chain. For each of these adducts, alkylation of the tertiary amine with MeI separately yielded stellettamide A (**13**, 95%) and its diastereoisomer. Characterization of each and comparison to natural material revealed that **13** was identical in all spectroscopic aspects (^{1}H- and ^{13}C-NMR in CD_3OD) and in chromatographic behavior (HPLC, 72% 20 mM KH_2PO_4, 28% ^{i}PrOH, *Sephadex C18*) with natural stellettamide A[7]). Measurement of the optical rotation revealed that **13** possessed the sign opposite to that reported for the natural product, leading to the conclusion that enantiomeric stellettamide A had been prepared by total synthesis.

Conclusion. – We have described an efficient synthesis of the unusual marine metabolite stellettamide A (**13**). The enantioselective route has allowed the absolute configuration of stellettamide A to be assigned unambiguously. The synthesis of the perhydroindolizine core utilizes a novel dipolar cycloaddition reaction between Me_3SiCHN_2 and a chiral dipolarophile to give an optically active Δ^1-pyrazoline. The strategy takes advantage of the functionality that is established in this step to produce all of stereogenic centers of the core. Importantly, the study expands further the synthetic elaborations available to the optically active pyrazoline adducts isolated from the dipolar cycloaddition reaction. Further applications of the dipolar cycloaddition reaction are currently being studied and will be the subject of future reports.

Experimental Part

General. Where appropriate, reagents were purified by standard procedures prior to use. Me_3SiCHN_2 was purchased from *Aldrich* as a 2M soln. in hexanes and used without purification. All non-aq. reactions were performed with oven-dried glassware under an atmosphere of dry N_2. Air- and moisture-sensitive liquids and solns. were transferred *via* syringe or stainless-steel cannula. Org. solns. were concentrated by rotary evaporation below 45° at *ca*. 25 mm Hg (water aspirator). THF was distilled from sodium benzophenone ketyl prior to use. ^{i}Pr$_3$N, Et$_3$N, CH_2Cl_2, and pyridine were distilled from CaH_2 prior to use. Benzene and toluene were distilled from Na prior to use. DMSO and DMF were distilled from CaH_2 and stored over 4-Å molecular sieves. Chromatographic purification was carried out by forced-flow chromatography on *Baker 7024-R* silica gel [20]. TLC was performed on *EM Reagents* 0.25-mm silica gel *60F* plates (230–400 mesh). Visualization of the developed plate was performed by fluorescence quenching, aq. ceric ammonium molybdate (CAM), ethanolic *p*-anisaldehyde or aq. $KMnO_4$ stains. NMR Spectra: *General Electric 300* spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C, resp., and a *Bruker AM-500* spectrometer operating at 500 MHz for ^{1}H; internal reference to residual proton-solvent signals; chemical shifts (δ) in ppm, coupling constants (J) in Hz. IR Spectra: *Perkin-Elmer Paragon 1000* spectrometer; NaCl plates or soln. cell; $\tilde{\nu}$ in cm^{-1}. M.p.: *Mel-Temp.* apparatus, uncorrected. High-resolution mass spectra (HR-MS): performed by UC Irvine and Caltech mass-spectral facilities. Optical rotations: *JASCO DIP-1000* digital polarimeter operating at 589 nm.

*(*S*)-4-[(*E*)-5-(Benzyloxy)pent-2-enoyl]-10,10-dimethyl-3λ⁶-thia-4-azatricyclo[5.2.1.0^{1,5}]decane-3,3-dione* (**19**). To a soln. of 5-(benzyloxy)pent-2-enoic acid [14] (7.1 g, 35 mmol) in CH_2Cl_2 (50 ml) at 0° was added oxalyl chloride (6.0 ml, 69 mmol), followed by DMF (4 drops). The soln. was stirred at 0° for 1 h and then at 23° for

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7) The iodide salt of **45** was dissolved in 25% MeOH/KH_2PO_4 and extracted with CH_2Cl_2 to give the putative monobasic phosphate salt, which was shown to be identical to stelletamide A by spectroscopic methods.

2 h. The solvent was evaporated to afford the crude acid chloride, which was used in the subsequent reaction without purification.

To a suspension of NaH (60% dispersion in mineral oil, 1.6 g, 41 mmol) in toluene (50 ml) at 23° was slowly added a soln. of (*S*)-camphorsultam (7.3 g, 35 mmol) in toluene (100 ml). The soln. was stirred at 23° for 2 h, and then a soln. of the acid chloride (35 mmol) in toluene (50 ml) was added, and the mixture was stirred at 23° for a further 2 h. H_2O (200 ml) was added, the layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3×150 ml). The combined org. layers were dried (Na_2SO_4) and concentrated under reduced pressure to a yellow oil. Purification by FC (silica gel; hexanes/AcOEt 5:1) afforded **19** (11.9 g, 87%). White solid. M.p. 83–85: TLC (hexanes/AcOEt 2:1): $R_f = 0.52$. $[\alpha]_D^{23} = -70.2$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3011, 2964, 1683, 1641, 1455, 1414, 1375, 1334, 1269, 1166, 1135, 1102, 1067, 993, 699. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.40–7.28 (*m*, 5 H); 7.14 (*dt*, $J = 15.0$, 6.9, 1 H); 6.66 (*dt*, $J = 15.1$, 1.4, 1 H); 4.54 (*s*, 2 H); 3.95 (*dd*, $J = 7.2$, 5.4, 1 H); 3.62 (*t*, $J = 6.5$, 2 H); 3.54 (*d*, $J = 13.8$, 1 H); 3.46 (*d*, $J = 13.8$, 1 H); 2.59 (*ddt*, $J = 6.5$, 6.5, 1.4, 2 H); 2.19–2.07 (*m*, 2 H); 2.00–1.86 (*m*, 3 H); 1.48–1.43 (*m*, 2 H); 1.19 (*s*, 3 H); 0.99 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 163.9; 147.2; 138.2; 128.5; 127.8; 127.7; 122.3; 73.1; 68.3; 65.2; 53.2; 48.5; 47.9; 44.7; 38.6; 33.0; 32.9; 26.6; 21.0; 20.0. HR-MS (FAB$^+$): 404.1896 ($[M+H]^+$, $C_{22}H_{29}NO_4S$; calc. 403.1817).

*Ethyl (4*R*,5*R*)-4-[2-(Benzyloxy)ethyl]-5-[1-[(*S*)-10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]-dec-4-yl]-carbonyl]-4,5-dihydropyrazole-1-carboxylate* (**22**). To a soln. of **19** (9.2 g, 23 mmol) in CH_2Cl_2 (60 ml)/hexanes (250 ml) was added powdered 4-Å molecular sieves (4.5 g), followed by Me_3SiCHN_2 (25.0 ml of 2M soln. in hexanes, 50.0 mmol), and the mixture was stirred at 23° for 90 h. The mixture was filtered, and the filtrate was concentrated to afford the intermediate cycloadduct. Integration of signals at 5.58 and 5.43 ppm in the ^{1}H-NMR ($CDCl_3$, 300 MHz) showed the adduct was formed as a mixture of diastereoisomers in a 93:7 ratio. This material was dissolved in CH_2Cl_2 (150 ml), cooled to 0°, and then EtO_2CCl (2.7 ml, 227 mmol) was added, followed by AgOTf (8.8 g, 34 mmol), and the mixture was stirred at 0° for 1.5 h. Sat. aq. $NaHCO_3$ soln. (100 ml) was added, the mixture was warmed to 23° and stirred vigorously for 15 min. The mixture was filtered through *Celite*, and the filter cake was washed thoroughly with CH_2Cl_2 (3×100 ml). H_2O (100 ml) was added to the combined filtrates, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×100 ml). The combined org. layers were dried (Na_2SO_4) and concentrated under reduced pressure to a yellow oil. Purification by FC (silica gel; hexanes/AcOEt 2:1) afforded **22** (8.4 g, 71%) and **23** (0.7 g, 6%). Pale yellow solids.

Data of **22**: M.p. 49–52°; TLC (hexanes/AcOEt 1:1): R_f 0.40. $[\alpha]_D^{26} = -128.9$ ($c = 0.86$, $CHCl_3$). IR ($CHCl_3$): 3012, 2965, 1697, 1435, 1384, 1337, 1272, 1240, 1135, 1067, 877, 699. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.38–7.28 (*m*, 5 H); 6.92 (*s*, 1 H); 5.05 (*d*, $J = 4.0$, 1 H); 4.52 (*d*, $J = 11.9$, 1 H); 4.47 (*d*, $J = 12.0$, 1 H); 4.30–4.24 (*m*, 2 H); 3.92 (*dd*, $J = 7.5$, 5.0, 1 H); 3.60–3.42 (*m*, 5 H); 2.32–2.17 (*m*, 2 H); 2.08–1.87 (*m*, 4 H); 1.47–1.30 (*m*, 6 H); 1.28 (*s*, 3 H); 1.00 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 168.7; 153.1; 148.7; 138.1; 128.5; 127.7; 127.7; 73.0; 67.5; 65.5; 63.0; 62.7; 53.1; 50.7; 49.4; 48.0; 44.5; 38.0; 32.7; 32.4; 26.6; 20.6; 20.0; 14.7. HR-MS (FAB$^+$): 518.2341 ($[M+H]^+$, calc. for $C_{26}H_{35}N_3O_6S^+$; calc. 517.2247).

Data of **23**: M.p. 51–53°. TLC (hexanes/AcOEt 1:1): R_f 0.40. $[\alpha]_D^{27} = +7.8$ ($c = 1.32$, $CHCl_3$). IR: 3030, 3018, 2965, 1701, 1436, 1384, 1342, 1272, 1239, 1138, 1066. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.38–7.26 (*m*, 5 H); 6.91 (*s*, 1 H); 5.10 (*d*, $J = 3.8$, 1 H); 4.52 (*d*, $J = 11.9$, 1 H); 4.46 (*d*, $J = 11.9$, 1 H); 4.44–4.23 (*m*, 2 H); 4.02–3.96 (*m*, 1 H); 3.58 (*t*, $J = 5.7$, 2 H); 3.53 (*s*, 2 H); 3.29–3.22 (*m*, 1 H); 2.30–2.21 (*m*, 1 H); 2.10–2.04 (*m*, 2 H); 2.00–1.84 (*m*, 4 H); 1.49–1.22 (*m*, 5 H); 1.11 (*s*, 3 H); 0.99 (*s*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 168.6; 153.0; 148.0; 138.1; 128.4; 127.6; 127.5; 72.7; 67.2; 65.1; 63.7; 62.7; 52.8; 50.5; 49.0; 47.8; 44.5; 38.0; 32.6; 32.1; 26.4; 20.9; 19.9; 14.6. HR-MS (FAB$^+$): 518.2337 ($[M+H]^+$, $C_{26}H_{35}N_3O_6S^+$; calc. 517.2247).

*Ethyl (4*S*,5*R*)-4-[2-(Benzyloxy)ethyl]-4,5-dihydro-5-(hydroxymethyl)pyrazole-1-carboxylate* (**24**). To a soln. of **22** (8.5 g, 16 mmol) in THF (200 ml) at −78° was added $LiAlH_4$ (66.0 ml of 1M soln. in THF, 66.0 mmol) slowly over 20 min. The soln. was stirred at −78° for 2 h, and then excess $LiAlH_4$ was quenched by careful addition of sat. aq. $NaHCO_3$ soln. (100 ml). The mixture was warmed to 23°, H_2O (100 ml) was added, and the mixture was extracted with CH_2Cl_2 (4×200 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure to a yellow oil. Purification (silica gel; hexanes/AcOEt 1:1 to 1:4) afforded (*S*)-camphorsultam (3.4 g, 95%) and **24** (4.5 g, 91%) as a colorless oil. TLC (AcOEt): $R_f = 0.51$. $[\alpha]_D^{20} = -21.2$ ($c = 1.24$, $CHCl_3$). IR (thin film): 3442, 2982, 2933, 2868, 1698, 1603, 1468, 1383, 1350, 1250, 1174, 1136, 1028, 827, 734, 700. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.41–7.28 (*m*, 5 H); 6.85 (*d*, $J = 1.5$, 1 H); 4.52 (*s*, 2 H); 4.33 (*q*, $J = 7.1$, 2 H); 4.09 (*ddd*, $J = 6.6$, 5.0, 4.4, 1 H); 3.75 (*dd*, $J = 5.0$, 4.4, 2 H); 3.64–3.56 (*m*, 2 H); 3.11–3.07 (*m*, 1 H); 1.99–1.91 (*m*, 1 H); 1.85–1.75 (*m*, 1 H); 1.39 (*t*, $J = 7.1$, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 154.8; 150.2; 137.8; 128.6; 127.9; 127.8; 73.3; 67.3; 64.9; 64.7; 62.9; 48.2; 32.1; 14.7. HR-MS (FAB$^+$): 307.1668 ($[M+H]^+$, $C_{16}H_{22}N_2O_4^+$; calc. 306.1580).

Ethyl (4S,5R)-4-[2-(Benzyloxy)ethyl]-5-formyl-4,5-dihydropyrazole-1-carboxylate (**25**). To a soln. of oxalyl chloride (2.6 ml, 29 mmol) in CH_2Cl_2 (100 ml) at $-78°$ was added a soln. of DMSO (4.2 ml, 59 mmol) in CH_2Cl_2 (40 ml) dropwise over 15 min. The soln. was stirred at $-78°$ for 15 min, and then a soln. of **24** (4.51 g, 14.7 mmol) in CH_2Cl_2 (60 ml) was added dropwise over 20 min. The mixture was stirred at $-78°$ for 20 min, and then Et_3N (10 ml, 73 mmol) was added slowly. The mixture was warmed slowly to 0°, and then aq. buffer soln. (pH 7, 100 ml) was added. After warming to 23°, the layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3×100 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure to a pale yellow oil. Purification by FC (silica gel; hexanes/AcOEt 1:1.5) afforded **25** (4.2 g, 93%). Colorless oil. TLC (hexanes/AcOEt 1:2): $R_f = 0.26$. $[\alpha]_D^{24} = -17.2$ ($c = 0.76$, $CHCl_3$). IR (thin film): 2982, 2932, 2865, 1736, 1695, 1603, 1486, 1469, 1433, 1383, 1350, 1175, 1143, 1115, 1028, 754, 700. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.61 (br. *s*, 1 H); 7.40–7.26 (*m*, 5 H); 6.85 (*s*, 1 H); 4.50 (*s*, 2 H); 4.51–4.48 (*m*, 1 H); 4.33 (*q*, $J = 6.5$, 2 H); 3.66–3.55 (*m*, 2 H); 3.46 (*ddd*, $J = 7.8, 7.8, 1.4, 1$ H); 2.07–1.96 (*m*, 1 H); 1.90–1.79 (*m*, 1 H); 1.36 (br. *m*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 196.7; 150.8; 149.1; 137.8; 128.5; 127.9; 127.9; 73.3; 68.8; 67.2; 62.9; 47.1; 31.7; 14.6. HR-MS (FAB$^+$): 305.1501 ($[M+H]^+$, $C_{16}H_{20}N_2O_4^+$; calc. 304.1423).

*Ethyl (4S,5R)-4-[2-(Benzyloxy)ethyl]-5-{(R)-4-[(*tert*-butyl)dimethylsilyloxy]-1-(methylsulfonyl)but-2-ynyl}-4,5-dihydropyrazole-1-carboxylate* (**28**). To a soln. of ^{t}BuMe$_2$SiOCH$_2$C≡CH (**26**; 3.42 g, 20.2 mmol) in THF at 0° was added BuMgCl (10.1 ml of 2M soln. in THF, 20.2 mmol), the mixture was then warmed to 23° for 30 min and then cooled to 0°. A soln. of **25** (1.23 g, 4.03 mmol) in THF (20 ml) was added dropwise over 10 min, then the reaction mixture was slowly warmed to 23° and stirred for 1 h. Sat. aq. $NaHCO_3$ soln. (50 ml) was added, the mixture was filtered, and the residue was washed thoroughly with CH_2Cl_2 (3×50 ml). The filtrate layers were separated, and the aq. layer was extracted with CH_2Cl_2 (2×50 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure to a pale yellow oil. This was dissolved in CH_2Cl_2 (25 ml), the resulting soln. was cooled to 0° and then Et_3N (0.84 ml, 6.1 mmol) and MsCl (0.47 ml, 6.1 mmol) were added. The soln. was stirred at 0° for 30 min, then H_2O (30 ml) was added. The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3×30 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure to a yellow oil. Purification by FC (silica gel; hexanes/AcOEt 3:1 to 2:1) afforded **28** (1.51 g, 68%). Colorless oil. TLC (hexanes/AcOEt 1:1): R_f 0.47 (major isomer), 0.39 (minor isomer). IR (thin film): 2982, 2982, 2863, 1738, 1695, 1604, 1470, 1436, 1383, 1350, 1175, 1143, 1127, 899, 838, 742, 700. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.40–7.29 (*m*, 5 H); 6.93 (*s*, 1 H, minor isomer); 6.91 (*d*, $J = 1.2$, 1 H, major isomer); 5.84 (br., 1 H); 4.57 (*d*, $J = 11.7$, 1 H, major isomer); 4.51 (*m*, 2 H, minor isomer); 4.50 (*d*, $J = 11.7$, 1 H, major isomer); 4.37–4.25 (*m*, 5 H); 3.66–3.55 (*m*, 3 H); 3.08 (*s*, 3 H, major isomer); 3.01 (*s*, 3 H, minor isomer); 1.98–1.80 (*m*, 2 H); 1.37 (*t*, $J = 7.1$, 3 H, major isomer); 1.36 (*t*, $J = 7.1$, 3 H, minor isomer); 0.91 (*s*, 9 H, minor isomer); 0.89 (*s*, 9 H, major isomer); 0.11 (*s*, 6 H, minor isomer); 0.09 (*s*, 6 H, major isomer). ^{13}C-NMR ($CDCl_3$, 75 MHz): 152.8; 150.3 (major isomer); 149.9 (minor isomer); 138.2 (major isomer); 138.0 (minor isomer); 128.5 (minor isomer); 128.5 (major isomer); 127.8 (minor isomer); 127.7 (major isomer); 127.6 (major isomer); 89.3 (minor isomer); 88.8 (major isomer); 77.8; 73.2 (minor isomer); 73.1 (major isomer); 69.3; 67.4 (minor isomer); 67.1 (major isomer); 64.4 (minor isomer); 63.7 (major isomer); 62.7; 51.4; 47.4; 39.0; 33.1 (minor isomer); 32.4 (major isomer); 25.7; 18.2 (minor isomer); 18.2 (major isomer); 14.7 (minor isomer); 14.6 (major isomer); −5.2. HR-MS (FAB$^+$): 553.2398 ($[M+H]^+$, $C_{26}H_{40}N_2O_7SSi^+$; calc. 552.2326).

*Ethyl (4S,5S)-4-[2(Benzyloxy)ethyl]-5-{4-[(*tert*-butyl)dimethylsilyloxy]but-2-ynyl}-4,5-dihydropyrazole-1-carboxylate* (**29**). To a suspension of HCO_2NH_4 (2.25 g, 35.8 mmol) and [Pd_2(dba)$_3$] (660 mg, 0.68 mmol) in benzene (100 ml) was added Bu_3P (710 µl, 2.72 mmol), and the resulting yellow suspension was stirred at 23° for 5 min. A soln. of **28** (3.76 g, 6.81 mmol) in benzene (50 ml) was then added, and the mixture was stirred at 23° for 48 h. The mixture was filtered, and evaporation of the filtrate under reduced pressure gave an orange oil. Purification by FC (silica gel; hexanes/AcOEt 2.5:1) afforded **29** (2.34 g, 76%) as a colorless oil, which was contaminated with a small quantity of the corresponding allene. Integration of the signals at 5.52–5.38 and 2.76–2.61 ppm indicated a 12:1 ratio in favor of **29**. TLC (hexanes/AcOEt 2:1): R_f 0.36. $[\alpha]_D^{24} = -2.7$ ($c = 0.54$, $CHCl_3$). IR (thin film): 2955, 2930, 2858, 2235, 1733, 1698, 1600, 1471, 1430, 1382, 1349, 1252, 1134, 1080, 837, 779, 734, 700. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.40–7.28 (*m*, 5 H); 6.86 (*s*, 1 H); 4.52 (*s*, 2 H); 4.34–4.26 (*m*, 4 H); 4.08–4.03 (*m*, 1 H); 3.59 (*m*, 2 H); 3.29–3.22 (*m*, 1 H); 2.76–2.61 (*m*, 2 H); 1.94–1.77 (*m*, 2 H); 1.36 (*t*, $J = 7.1$, 3 H); 0.91 (*s*, 9 H); 0.11 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 152.7; 149.5; 138.0; 128.4; 127.6; 127.5; 81.1; 79.9; 73.0; 67.4; 62.0; 60.5; 51.7; 50.0; 32.4; 25.8; 23.1; 18.2; 14.6; −5.1.

*Ethyl (4S,5S)-4-[2-(Benzyloxy)ethyl]-5-{(Z)-5-[(*tert*-butyl)dimethylsilyloxy]but-2-enyl}-4,5-dihydropyrazole-1-carboxylate* (**30**). To a soln. of **29** (2.33 g, 5.07 mmol) in MeOH (30 ml) was added quinoline (0.5 ml) and 5% Pd/$BaSO_4$ (100 mg), and the mixture was stirred under an atmosphere of H_2 at 23° for 5 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure to a pale yellow oil. Purification by FC

(silica gel; CH_2Cl_2/Et_2O 10:1) afforded **30** (2.19 g, 95%). Colorless oil. TLC (CH_2Cl_2/Et_2O 10:1): R_f 0.36. $[\alpha]_D^{22} = -4.0$ ($c = 0.46$, $CHCl_3$). IR (thin film): 2955, 2930, 2857, 1732, 1698, 1598, 1472, 1429, 1382, 1349, 1252, 1134, 837, 777, 738, 699. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.40–7.28 (*m*, 5 H); 6.82 (*s*, 1 H); 5.74–5.66 (*m*, 1 H); 5.38–5.30 (*m*, 1 H); 4.50 (*s*, 2 H); 4.30 (*q*, $J = 7.2$, 2 H); 4.21 (*d*, $J = 6.2$, 2 H); 4.06–4.01 (*m*, 1 H); 3.61–3.50 (*m*, 2 H); 3.03–2.97 (*m*, 1 H); 2.59–2.37 (*m*, 2 H); 1.89–1.63 (*m*, 2 H); 1.37 (*t*, $J = 7.2$, 3 H); 0.91 (*s*, 9 H); 0.07 (*s*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 152.8; 150.0; 138.0; 133.6; 128.5; 127.8; 127.7; 124.0; 73.2; 67.3; 62.1; 61.4; 59.3; 49.2; 32.4; 30.6; 26.0; 18.4; 14.7; −5.2. HR-MS (FAB$^+$): 461.2843 ([$M+H$], $C_{25}H_{40}N_2O_4Si^+$; calc. 460.2757).

tert-*Butyl (4*S*,5*S*)-4-[2-(Benzyloxy)ethyl]-4,5-dihydro-5-[(*Z*)-5-hydroxypent-2-enyl]pyrazole-1-carboxylate* (**32**). A mixture of **30** (2.19 g, 4.76 mmol) and $Ba(OH)_2$ (7.5 g, 24 mmol) in dioxane (140 ml)/H_2O (95 ml) was heated to 100° for 2 h. The mixture was cooled to 23°, acidified to pH 3, and washed with Et_2O (30 ml). The org. washing was discarded, and the aq. layer was basified to pH 12, and extracted with CH_2Cl_2 (6 × 50 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude alcohol was dissolved in THF (100 ml)/H_2O (100 ml), then $(Boc)_2O$ (5.2 g, 24 mmol) and NaOH (0.9 g, 24 mmol) were added, and the mixture was stirred at 23° for 6 h. The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 100 ml). The combined org. layers were dried (Na_2SO_4) and concentrated under reduced pressure to a pale yellow oil. Purification by FC (silica gel; hexanes/AcOEt 1:3) afforded **32** (1.43 g, 80%). Colorless oil. TLC (hexanes/AcOEt 1:3): R_f 0.31. $[\alpha]_D^{24} = +14.5$ ($c = 0.50$, $CHCl_3$). IR (thin film): 3452, 2978, 2932, 2864, 1694, 1599, 1479, 1455, 1394, 1368, 1249, 1148, 1028, 863, 829, 749, 699. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.41–7.29 (*m*, 5 H); 6.76 (*d*, $J = 1.6$, 1 H); 5.83–5.74 (*m*, 1 H); 5.50–5.41 (*m*, 1 H); 4.53 (*d*, $J = 12.1$, 1 H); 4.48 (*d*, $J = 12.0$, 1 H); 4.19–4.12 (*m*, 2 H); 4.00–3.95 (*m*, 1 H); 3.59–3.49 (*m*, 2 H); 3.04–2.97 (*m*, 1 H); 2.51–2.44 (*m*, 2 H); 1.90–1.60 (*m*, 2 H); 1.56 (*s*, 9 H). ^{1}H-NMR ($CDCl_3$, 75 MHz): 152.0; 149.2; 137.9; 133.0; 128.5; 127.8; 127.8; 125.2; 81.5; 73.1; 67.2; 61.3; 58.1; 49.1; 32.2; 30.7; 28.4. HR-MS (FAB$^+$): 375.2288 ([$M+H$]$^+$, $C_{21}H_{30}N_2O_4^+$; calc. 374.2206).

*(1*S*,8a*S*)-1-[2-(Benzyloxy)ethyl]-1,5,8,8a-tetrahydro-pyrazolo[1,5-*a*]pyridine* (**35**). To a soln. of **32** (500 mg, 1.34 mmol) in CH_2Cl_2 (15 ml) at 0° was added Et_3N (280 µl, 2.00 mmol), followed by MsCl (155 µl, 2.00 mmol). The soln. was stirred at 0° for 30 min, and then H_2O (30 ml) was added. The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 30 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure to a pale yellow oil. This was dissolved in dioxane (40 ml) and added dropwise to a soln. of 10% H_2SO_4 in dioxane (40 ml) over 15 min. The mixture was stirred at 23° for 15 min and then added dropwise to an aq. soln. of NaOH (50 ml of 2M, 100 mmol) over 10 min. After stirring for a further 15 min, AcOEt (50 ml) was added, the layers were separated, and the aq. layer was extracted with CH_2Cl_2 (2 × 40 ml). The combined org. layers were dried (Na_2SO_4) and concentrated under reduced pressure to an orange oil. Purification by FC (silica gel; hexanes/AcOEt 1:1) afforded **35** (285 mg, 83%). Yellow oil. TLC (hexanes/AcOEt 1:1): R_f 0.57. $[\alpha]_D^{24} = -135.0$ ($c = 1.10$, $CHCl_3$). IR (thin film): 3032, 2928, 2792, 1644, 1561, 1496, 1454, 1363, 1101, 1039, 945, 738, 698. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.41–7.28 (*m*, 5 H); 6.84 (*d*, $J = 1.1$, 1 H); 5.83–5.73 (*m*, 2 H); 4.54 (*s*, 2 H); 4.11 (*dd*, $J = 15.9$, 2.5, 1 H); 3.66–3.55 (*m*, 2 H); 3.46–3.37 (*m*, 1 H); 2.85–2.75 (*m*, 1 H); 2.62–2.52 (*m*, 1 H); 2.32–2-27 (*m*, 2 H); 2.00–1.77 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 147.6; 138.2; 128.5; 127.7; 127.7; 125.5; 125.4; 73.1; 68.3; 67.4; 52.1; 49.7; 30.3; 30.1. HR-MS (CI$^+$): 256.1570 (M^+, $C_{16}H_{20}N_2O^+$; calc. 256.1576).

*(*S*)-*N*-[(*R*)-4-(Benzyloxy)-2-(piperidin-2-yl)butyl]-2,2,2-trifluoroacetamide* (**37**). *Raney*-Ni (cat. amount) was washed with EtOH (5 × 2 ml), suspended in EtOH (10 ml), and added to a flask containing **35** (100 mg, 0.39 mmol). The mixture was then stirred under an atmosphere of H_2 at 23° for 36 h. The mixture was filtered through *Celite*, and the filtrate was concentrated under reduced pressure to give the crude amine. This was dissolved in THF (10 ml), cooled to 0°, and CF_3COOEt (46 µl, 0.39 mmol) was added. The mixture was stirred at 0° for 1 h and then at 23° for 1 h. The solvent was then evaporated under reduced pressure to give a pale yellow oil. Purification by FC (silica gel; MeOH) afforded **37** (119 mg, 85%). Colorless oil. TLC (MeOH): R_f 0.29. $[\alpha]_D^{24} = +4.8$ ($c = 0.48$, $CHCl_3$). IR (thin film): 2934, 2856, 1716, 1547, 1454, 1363, 1331, 1156, 1103, 885, 738, 699. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.87–9.80 (br., 1 H); 7.41–7.29 (*m*, 5 H); 4.52 (*s*, 2 H); 3.55 (*t*, $J = 5.8$, 2 H); 3.43 (*d*, $J = 3.5$, 2 H); 3.10–3.04 (*m*, 1 H); 2.69–2.63 (*m*, 1 H); 2.49 (*dt*, $J = 11.6$, 2.8, 1 H); 1.90–1.51 (*m*, 7 H); 1.43–1.22 (*m*, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 157.3 (*q*, $J = 37$); 137.9; 128.5; 128.5; 127.9; 116.2 (*q*, $J = 288$); 73.3; 68.1; 59.6; 47.1; 41.5; 38.6; 30.1; 29.6; 26.3; 24.8. HR-MS (CI$^+$): 359.1946 ([$M+H$]$^+$, $C_{18}H_{25}F_3N_2O_2^+$; calc. 358.1868).

*(*S*)-2,2,2-Trifluoro-*N*-[(*R*)-4-hydroxy-2-(piperidin-2-yl)butyl]acetamide* (**38**). To a soln. of **37** (53 mg, 0.15 mmol) in MeOH (3 ml) was added HCO_2NH_4 (53 mg, 0.84 mmol), followed by 20% $Pd(OH)_2$/C (15 mg), and the mixture was heated to reflux for 1 h. The mixture was cooled to 23°, filtered through *Celite*, and the

filtrate was concentrated to a pale yellow oil. Purification by FC (silica gel; MeOH) afforded **38** (33 mg, 85%). Colorless oil. TLC (MeOH): R_f 0.25. $[\alpha]_D^{24} = +1.1$ ($c = 1.05$, $CHCl_3$). IR (thin film): 2935, 1715, 1558, 1446, 1331, 1154, 1054, 895, 800, 723. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.15–8.10 (br., 1 H); 3.90–3.72 (*m*, 2 H); 3.59 (*dd*, $J =$ 13.9, 4.8, 1 H); 3.45 (*dd*, $J = 13.9$, 5.4, 1 H); 3.26–3.22 (*m*, 1 H); 2.91–2.47 (*m*, 4 H); 1.99–1.37 (*m*, 9 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 157.5 (*q*, $J = 37$); 116.1 (*q*, $J = 288$); 60.6; 58.8; 47.1; 42.1; 41.9; 31.8; 27.8; 25.9; 24.6. HR-MS (CI^+) calc. for $C_{11}H_{19}F_3N_2O_2$ 268.1399, found: 269.1477 $(M+H)^+$.

2,2,2-Trifluoro-N-*[(1*R,*8a*S*)-1-(1,2,3,5,6,7,8,8a-octahydroindolizin-1-yl)methyl]acetamide* (**39**). To a soln. of **38** (75 mg, 0.28 mmol) in MeCN (15 ml) at 0° was added Et_3N (85 µl, 0.62 mmol) and CBr_4 (102 mg, 0.31 mmol), followed by Ph_3P (81 mg, 0.31 mmol). The mixture was stirred at 0° for 5 min, 23° for 5 min, then the soln. was concentrated to a yellow oil. Purification by FC (silica gel; AcOEt/MeOH 2 : 1) afforded **39** (53 mg, 75%). Colorless oil; TLC (MeOH): R_f 0.38. $[\alpha]_D^{27} = +60.0$ ($c = 0.32$, $CHCl_3$). IR ($CHCl_3$): 3022, 2941, 2811, 1716, 1546, 1472, 1444, 1370, 1343, 1335, 1182, 1109. ^{1}H-NMR ($CDCl_3$, 300 MHz): 9.41 (br., 1 H); 3.37 (*ddd*, $J =$ 13.5, 3.2, 0.9, 1 H); 3.24 (*dd*, $J = 13.6$, 1.0, 1 H); 3.14–3.16 (*m*, 2 H); 2.36–2.29 (*m*, 1 H); 2.15–1.97 (*m*, 3 H); 1.90–1.74 (*m*, 3 H); 1.69–1.61 (*m*, 1 H); 1.58–1.18 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 157.5 (*q*, $J = 37$); 116.1 (*q*, $J = 288$); 66.0; 53.4; 42.6; 37.0; 26.3; 25.9; 25.2; 23.9. HR-MS (CI^+): 249.1215 ($[M-H]^+$; $C_{11}H_{17}F_3N_2O^+$; calc. 250.1293).

*(2*R,*5*E,*9*E*)*-N-*[(1*S,*2*S*)-2-Hydroxy-1-methyl-2-phenylethyl]-2,6,10,*N*-tetramethylundeca-5,9-dienamide* (**43**). In a 200-ml flask, LiCl (1.28 g, 30.2 mmol) was dried under high vacuum with a *Bunsen* burner for 10 min and then cooled under N_2. $^iPr_2NH$ (3.1 ml, 22 mmol) was added along with THF (50 ml), and the suspension was cooled to −78°. BuLi (12.5 ml of 1.6M soln. in hexanes, 20 mmol) was added slowly, and the mixture was warmed briefly to 0° and then recooled to −78°. A soln. of the auxiliary-bound propionate [18] (2.2 g, 9.8 mmol) in THF (25 ml) was added dropwise, the mixture was then stirred at −78° for 1 h and then slowly warmed to 23° for 5 min before being cooled to 0°. To this was added a soln. of homogeranyl iodide (**42**) [21] (1.4 g, 5 mmol) in THF (25 ml) dropwise, the resulting soln. was stirred at 0° for 3 h before the addition of sat. aq. NH_4Cl (100 ml). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml), the combined org. layers were dried (Na_2SO_4) and concentrated under reduced pressure to a pale yellow oil. Purification by FC (silica gel; hexanes/AcOEt 1 : 1) afforded **43** (1.7 g, 92%). Colorless oil. TLC (hexanes/AcOEt 2 : 1): R_f 0.31. $[\alpha]_D^{26} = +44.8$ ($c = 0.51$, $CHCl_3$; (*R*)-enantiomer), $[\alpha]_D^{25} = -44.8$ ($c = 0.50$, $CHCl_3$; (*S*)-enantiomer). IR (thin film): 3418, 2969, 1741, 1615, 1455, 1410, 1375, 1109, 1084, 1051, 834, 757, 700. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.41–7.25 (*m*, 5 H); 5.10–5.04 (*m*, 2 H); 4.64–4.10 (*m*, 3 H); 2.85 (*s*, 3 H); 2.67–2.60 (*m*, 1 H); 2.21–1.91 (*m*, 6 H); 1.69 (*s*, 3 H); 1.61 (*s*, 3 H); 1.57 (*s*, 3 H); 1.42–1.33 (*m*, 2 H); 1.15–1.07 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 178.8; 177.7 (rotamer); 142.6; 141.8 (rotamer); 135.7; 135.3 (rotamer); 131.4; 131.3 (rotamer); 128.6 (rotamer); 128.3; 128.1 (rotamer); 127.5; 127.0 (rotamer); 126.4; 124.4 (rotamer); 124.3; 123.9; 76.3; 75.4 (rotamer); 57.9; 39.8 (rotamer); 39.8; 35.7; 35.3 (rotamer); 33.9; 33.9 (rotamer); 26.8 (rotamer); 26.7; 25.8; 25.6; 17.8 (rotamer); 17.8; 16.0; 15.6 (rotamer); 14.5; 14.3 (rotamer). HR-MS (FAB^+): 372.2896 ($[M+H]^+$, $C_{24}H_{37}NO_2^+$; calc. 371.2824).

*(2*R,*5*E,*9*E*)-2,6,10-Trimethylundeca-5,9-dien-1-ol* (**44**). To a soln. of $^iPr_2NH$ (3.3 ml, 18 mmol) in THF (50 ml) at −78° was added BuLi (11.2 ml of 1.6M soln. in hexanes, 18 mmol), the soln. was then briefly warmed to 0° before being recooled to −78°. $BH_3 \cdot NH_3$ (0.59 g, 19 mmol) was added in one portion, the mixture was warmed to 0° and stirred for 20 min, then warmed to 23° and stirred for a further 20 min, before being cooled to 0°. To this was slowly added a soln. of **43** (1.63 g, 4.4 mmol) in THF (50 ml) over 10 min. The mixture was warmed to 23° and stirred for 4 h. Excess $BH_3 \cdot NH_3$ was quenched by careful addition of 2M HCl (100 ml), the layers were then separated, and the aq. layer was extracted with Et_2O (2 × 50 ml). The combined org. layers were dried (Na_2SO_4) and concentrated under reduced pressure to a pale yellow oil. Purification by FC (silica gel; hexanes/AcOEt 1 : 1) afforded **44** (0.84 g, 91%). Colorless oil. TLC (hexanes/AcOEt 4 : 1): R_f 0.32. $[\alpha]_D^{28} = +8.1$ ($c = 0.40$, $CHCl_3$, (*R*)-enantiomer); $[\alpha]_D^{25} = -9.8$ ($c = 1.00$, $CHCl_3$; (*S*)-enantiomer). IR (thin film): 3334, 2965, 2924, 1670, 1453, 1377, 1107, 1041, 986, 832. ^{1}H-NMR ($CDCl_3$, 300 MHz): 5.14–5.06 (*m*, 2H); 3.54–3.41 (*m*, 2 H); 2.10–1.94 (*m*, 6 H); 1.67 (*d*, $J = 1.0$, 3 H); 1.60 (*s*, 6 H); 1.55–1.39 (*m*, 1 H); 1.30 (*t*, $J = 5.6$, 1 H); 1.21–1.12 (*m*, 1 H); 0.93 (*d*, $J = 6.7$, 3 H). ^{1}H-NMR ($CDCl_3$, 75 MHz): 134.9; 131.2; 124.6; 124.4; 68.0; 39.8; 35.3; 33.3; 26.7; 25.7; 25.4; 17.7; 16.6; 16.0. HR-MS (EI^+): 210.1976 (M^+, $C_{14}H_{26}O^+$; calc. 210.1984).

*Ethyl (*R,*2*E,*7*E*)-4,8,12-Trimethyltrideca-2,7,11-trienoate* (**46**). To a soln. of oxalyl chloride (0.56 ml, 5.2 mmol) in CH_2Cl_2 (15 ml) at −78° was added DMSO (1.03 ml, 14.4 mmol). The soln. was stirred at −78° for 5 min, and then a soln. of **44** (0.76 g, 3.6 mmol) in CH_2Cl_2 (15 ml) was added dropwise over 10 min. The mixture was stirred at −78° for 15 min, and then Et_3N (2.5 ml, 18 mmol) was added slowly. The mixture was warmed slowly to 0°, and then aq. buffer soln. (pH 7; 20 ml) was added. After warming to 23°, the layers were separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 20 ml). The combined org. extracts were washed with 2M

HCl (30 ml), sat. $NaHCO_3$ soln. (30 ml), then dried (Na_2SO_4), and concentrated under reduced pressure to a pale yellow oil. The crude aldehyde was dissolved in CH_2Cl_2 (30 ml), and $Ph_3PCHCOOEt$ (5.1 g, 14 mmol) was added in one portion, and the mixture was stirred at 23° for 24 h. The solvent was evaporated under reduced pressure, and pentane (50 ml) was added to the residue. Precipitated triphenylphosphine oxide was filtered off and washed with pentane (2 × 50 ml), and the filtrate was concentrated under reduced pressure to a yellow oil. Purification by FC (silica gel; hexanes/AcOEt 20:1) afforded **46** (0.79 g, 79%). Colorless oil. TLC (hexanes/AcOEt 15:1): R_f 0.30. $[\alpha]_D^{24} = -46.9$ ($c = 0.88$, $CHCl_3$; (*R*)-enantiomer); $[\alpha]_D^{23} = +46.2$ ($c = 1.00$, $CHCl_3$; (*S*)-enantiomer). IR (thin film): 2966, 2927, 2855, 1723, 1652, 1451, 1368, 1301, 1267, 1178, 1039, 985. ^{1}H-NMR ($CDCl_3$, 300 MHz): 6.86 (*dd*, *J* = 15.7, 8.0, 1 H); 5.77 (*dd*, *J* = 15.7, 1.1, 1 H); 5.10–5.05 (*m*, 2 H); 4.18 (*q*, *J* = 7.1, 2 H); 2.34–2.29 (*m*, 1 H); 2.08–1.94 (*m*, 6 H); 1.68 (*d*, *J* = 0.7, 3 H); 1.60 (*s*, 3 H); 1.58 (*d*, *J* = 0.8, 3 H); 1.45–1.36 (*m*, 2 H); 1.29 (*t*, *J* = 7.1, 3 H); 1.05 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.8; 154.5; 135.4; 131.2; 124.3; 123.9; 119.7; 60.1; 39.7; 36.0; 36.0; 26.6; 25.8; 25.5; 19.4; 17.7; 16.0; 14.3. HR-MS (EI$^+$): 278.2257 (M^+, $C_{18}H_{30}O_2^+$; calc. 278.2246).

*(R,2*E*,7*E*)-4,8,12-Trimethyltrideca-2,7,11-trienoic Acid* (**47**). A mixture of **46** (250 mg, 0.90 mmol) and LiOH (114 mg, 2.70 mmol) in H_2O (3 ml)/THF, (5 ml) was heated to reflux for 12 h. The mixture was cooled to 23°, then acidified to pH 3, and extracted with CH_2Cl_2 (3 × 20 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure to a pale yellow oil. Purification by FC (silica gel; hexanes/AcOEt 2:1) afforded **47** (210 mg, 94%). Colorless oil. TLC (hexanes/AcOEt 2:1): R_f 0.45. $[\alpha]_D^{28} = -47.9$ (c = 0.55, $CHCl_3$; (*R*)-enantiomer); $[\alpha]_D^{25} = +48.2$ ($c = 0.45$, $CHCl_3$; (*S*)-enantiomer). IR (thin film): 2914, 2682, 1694, 1651, 1418, 1284, 1217, 986, 937, 687. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.00 (*dd*, *J* = 15.7, 8.0, 1 H); 5.80 (*dd*, *J* = 15.7, 1.1, 1 H); 5.11–5.07 (*m*, 2 H); 2.40–2.35 (*m*, 1 H); 2.12–1.96 (*m*, 6 H); 1.69 (*d*, *J* = 0.8, 3 H); 1.62 (*s*, 3 H); 1.560 (*s*, 3 H); 1.50–1.38 (*m*, 2 H); 1.09 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 172.6; 157.3; 135.4; 131.1; 124.4; 123.6; 119.1; 39.6; 36.0; 35.9; 26.5; 25.6; 25.4; 19.1; 17.6; 15.9. HR-MS (EI$^+$): 250.1941 (M^+, $C_{16}H_{26}O_2^+$; calc. 250.1933).

*(*R*,2*E*,7*E*)-4,8,12-Trimethyl*-N-*{[(1*R*,8a*S*)-1,2,3,5,6,7,8,8a-octahydroindolizin-1-yl]methyl}trideca-2,7,11-trienamide* (**48**). The trifluoroacetamide **39** (45 mg, 0.18 mmol) was dissolved in 5% K_2CO_3 in MeOH/H_2O (15 ml), and the soln. was stirred at 23° for 4 h. H_2O (3 ml) was added, the soln. was saturated with NaCl, and then extracted with CH_2Cl_2 (5 × 15 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford crude **40**. This was dissolved in CH_2Cl_2 (5 ml) and added to a flask containing a soln. of the (*R*)-enantiomer of **47** (67 mg, 0.27 mmol) in CH_2Cl_2 (5 ml). DCC (72 mg, 0.36 mmol) and DMAP (2 mg, cat.) were then added, and the mixture was stirred at 23° for 4 h. Evaporation of the solvent to a pale yellow oil, and purification by FC (silica gel; AcOEt to AcOEt/MeOH 2:1) afforded **48** (50 mg, 72%). White solid. M.p. 61–63°. TLC (MeOH): R_f 0.36. $[\alpha]_D^{27} = +9.5$ ($c = 0.30$, $CHCl_3$). IR (thin film): 3286, 3078, 2931, 2855, 2784, 1668, 1628, 1552, 1450, 1376, 1263, 1149, 1111, 983. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.45–7.36 (br., 1 H); 6.66 (*dd*, *J* = 15.4, 7.2, 1 H); 5.70 (*dd*, *J* = 15.4, 0.8, 1 H); 5.12–5.07 (*m*, 2 H); 3.43 (*ddd*, *J* = 13.4, 5.9, 3.9, 1 H); 3.23–3.06 (*m*, 3 H); 2.34–2.27 (*m*, 2 H); 2.12–1.96 (*m*, 10 H); 1.93–1.64 (*m*, 3 H); 1.69 (*d*, *J* = 0.8, 3 H); 1.62 (*s*, 3 H); 1.60 (*s*, 3 H); 1.57–1.19 (*m*, 6 H); 1.05 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.7; 148.8; 135.3; 131.4; 124.4; 124.2; 122.8; 66.4; 54.0; 53.8; 42.0; 39.8; 37.9; 36.3; 35.9; 26.7; 26.4; 25.9; 25.8; 25.6; 25.4; 24.2; 19.9; 17.8; 16.1. HR-MS (CI$^+$): 386.3289 (M^+, $C_{25}H_{42}N_2O^+$; calc. 386.3297).

*(S,2*E*,7*E*)-4,8,12-Trimethyl*-N-*{[(1*R*,8a*S*)-1,2,3,5,6,7,8,8a-octahydroindolizin-1-yl]methyl}trideca-2,7,11-trienamide* (**49**). The trifluoroacetamide **39** (25 mg, 0.10 mmol) was dissolved in 5% K_2CO_3 in MeOH/H_2O (7 ml), and the soln. was stirred at 23° for 4 h. H_2O (1 ml) was added, the soln. was saturated with NaCl, and then extracted with CH_2Cl_2 (5 × 10 ml). The combined org. extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford crude **40**. This was dissolved in CH_2Cl_2 (5 ml) and added to a flask containing a soln. of the (*S*)-enantiomer of **47** (40 mg, 0.16 mmol) in CH_2Cl_2 (5 ml). DCC (43 mg, 0.20 mmol) and DMAP (2 mg, cat.) were then added, and the mixture was stirred at 23° for 4 h. Evaporation of the solvent to a pale yellow oil and purification by FC (silica gel; AcOEt to AcOEt/MeOH 2:1) afforded **49** (27 mg, 70%). White solid. M.p. 51–52°. TLC (MeOH): R_f 0.36. $[\alpha]_D^{25} = +65.3$ ($c = 0.33$, $CHCl_3$). IR (thin film): 3286, 3078, 2930, 2855, 2783, 1668, 1627, 1557, 1450, 1376, 1342, 1330, 1273, 1233, 1149, 1112. ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.38–7.26 (br., 1 H); 6.66 (*dd*, *J* = 15.4, 7.9, 1 H); 5.70 (*d*, *J* = 15.4, 1 H); 5.16–5.11 (*m*, 2 H); 3.49 (*ddd*, *J* = 13.5, 6.0, 4.2, 1 H); 3.27–3.14 (*m*, 3 H); 2.42–2.29 (*m*, 2 H); 2.20–2.00 (*m*, 10 H); 1.97–1.77 (*m*, 3 H); 1.73 (*s*, 3 H); 1.66 (*s*, 3 H); 1.63 (*s*, 3 H); 1.61–1.24 (*m*, 6 H); 1.09 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.7; 148.7; 135.3; 131.4; 124.4; 124.2; 123.0; 66.5; 54.3; 53.9; 42.2; 39.8; 37.8; 36.4; 35.9; 26.7; 26.6; 26.0; 25.8; 25.7; 25.7; 24.3; 19.9; 17.8; 16.1. HR-MS (CI$^+$): 386.3289 (M^+, $C_{25}H_{42}N_2O^+$; calc. 386.3297).

*(1*R*,8a*S*)-1,2,3,5,6,7,8,8a-Octahydro-4-methyl-1-{[(*R*,2*E*,7*E*)-4,8,12-trimethyltrideca-2,7,11-trienylamino]-methyl}indolizinium Iodide* (*ent*-**13**). To a soln. of **48** (43 mg, 0.11 mmol) in MeOH (4 ml) was added $KHCO_3$

(100 mg, 1 mmol) and MeI (300 µl, 5 mmol), and the mixture was stirred at 23° for 5 h. Filtration and evaporation of the solvent under reduced pressure afforded *ent*-**13** (53 mg, 95%). Pale yellow solid. M.p. 105–110°. $[\alpha]_D^{28} = -26.3$ ($c = 0.45$, $CHCl_3$). IR (thin film): 3453, 3258, 3074, 2928, 1667, 1632, 1564, 1548, 1451, 1377, 1342, 1278, 1227, 945, 731. ^{1}H-NMR (CD_3OD, 500 MHz): 6.70 (*dd*, *J* = 15.5, 8.0, 1 H); 5.89 (*dd*, *J* = 15.5, 1.0, 1 H); 5.11–5.08 (*m*, 2 H); 3.91 (*ddd*, *J* = 11.8, 11.8, 7.2, 1 H); 3.69 (*ddd*, *J* = 11.7, 5.9, 3.6, 1 H); 3.60 (br. *d*, *J* = 13.5, 1 H); 3.46–3.32 (*m*, 4 H); 3.15 (*s*, 3 H); 31.3–3.07 (*m*, 1 H); 2.46–2.36 (*m*, 1 H); 2.34–2.28 (*m*, 1 H); 2.09–2.05 (*m*, 1 H); 2.03–1.96 (*m*, 5 H); 1.91–1.89 (*m*, 4 H); 1.87–1.81 (*m*, 2 H); 1.66 (*s*, 3 H); 1.64–1.61 (*m*, 1 H); 1.59 (*s*, 3 H); 1.58 (*s*, 3 H); 1.55–1.50 (*m*, 1 H); 1.43–1.38 (*m*, 2 H); 1.04 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR (CD_3OD, 75 MHz): 168.9; 151.5; 136.4; 132.1; 125.4; 125.3; 123.0; 73.9; 61.2; 57.9; 54.5; 40.8; 40.5; 39.7; 37.5; 37.0; 27.7; 26.6; 25.9; 25.2; 23.3; 21.5; 21.1; 20.0; 17.8; 16.2. HR-MS (FAB$^+$): 401.3542 ($M - I$)$^+$, $C_{26}H_{45}IN_2O^+$; calc. 528.2577).

*(1*R*,8a*S*)-1,2,3,5,6,7,8,8a-Octahydro-4-methyl-1-{[(*S*,2*E*,7)-4,8,12-trimethyltrideca-2,7,11-trienoylamino]methyl}indolizinium Iodide* (**13**). To a soln. of **49** (22 mg, 0.06 mmol) in MeOH (2 ml) was added $KHCO_3$ (50 mg, 0.5 mmol) and MeI (150 µl, 2.5 mmol), and the mixture was stirred at 23° for 5 h. Filtration and evaporation of the solvent under reduced pressure afforded **13** (27 mg, 93%). Pale yellow solid. M.p. 105–110°. $[\alpha]_D^{28} = +20.2$ ($c = 0.14$, $CHCl_3$). IR (thin film): 3266, 2926, 1668, 1631, 1543, 1451, 1376, 1276, 1226, 985. ^{1}H-NMR (CD_3OD, 500 MHz): 6.70 (*dd*, *J* = 15.6, 8.0, 1 H); 5.89 (*dd*, *J* = 15.4, 1.0, 1 H); 5.11–5.06 (*m*, 2 H); 3.91 (*ddd*, *J* = 11.6, 11.6, 7.3, 1 H); 3.70 (*ddd*, *J* = 11.8, 5.9, 3.6, 1 H); 3.60 (br. *d*, *J* = 13.4, 1 H); 3.46–3.40 (*m*, 2 H); 3.36–3.32 (*m*, 2 H); 3.16 (*s*, 3 H); 3.13–3.06 (*m*, 1 H); 2.46–2.38 (*m*, 1 H); 2.34–2.28 (*m*, 1 H); 2.09–2.03 (*m*, 1 H); 2.00–1.96 (*m*, 5 H); 1.91–1.90 (*m*, 4 H); 1.87–1.83 (*m*, 2 H); 1.66 (*d*, *J* = 0.8, 3 H); 1.64–1.61 (*m*, 1 H); 1.59 (*s*, 3 H); 1.58 (*s*, 3 H); 1.55–1.51 (*m*, 1 H); 1.46–1.36 (*m*, 2 H); 1.04 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR (CD_3OD, 75 MHz): 169.0; 151.6; 136.4; 132.3; 125.4; 125.3; 122.9; 73.9; 61.2; 57.8; 54.5; 40.8; 40.5; 39.7; 37.4; 37.0; 27.7; 26.6; 25.9; 25.2; 23.3; 21.6; 21.1; 20.0; 17.8; 16.2; HR-MS (FAB$^+$): 401.3532 ([$M - I$]$^+$, $C_{26}H_{45}IN_2O^+$; calc. 528.2577).

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