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Note

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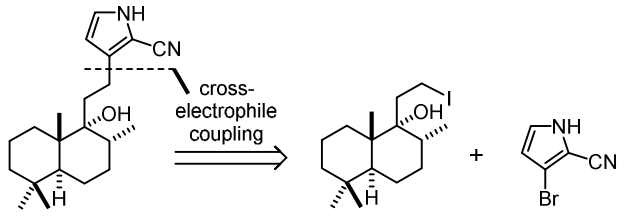
Synthesis of (+)-Vitepyrroloid A and (+)-Vitepyrroloid B by Late-Stage Ni-Catalyzed C(sp2)-C(sp3) Cross-Electrophile Coupling

Martina Menger, Dieter Lentz, and Mathias Christmann*

Freie Universität Berlin, Institute of Chemistry and Biochemistry, Takustr. 3, 14195 Berlin, Germany

Supporting Information Placeholder



ABSTRACT: A concise and scalable five-step synthesis of vitepyrroloids A and B, two cytotoxic labdane diterpenoid alkaloids from *Vitex trifolia*, is presented. The presented approach features a Ni-catalyzed cross-electrophile coupling between a (+)-sclareolide-derived alkyl iodide and 3-bromo-2-cyanopyrrole.

Several species of the *Vitex* genus within the *Lamiaceae* family are used in traditional medicines for treatment in various therapeutic indications. In 2017, Zhao and Gu reported the isolation of four cytotoxic diterpenoid alkaloids from the dried leaves of *Vitex trifolia* L. (Verbenaceae), a small deciduous shrub that is broadly distributed in South China.[1] Vitepyrroloids A–C (**1**–**3**, Figure 1) and D (not shown) share an unprecedented 2-cyanopyrrole labdane core and differentiate in both the oxidation pattern of the decalin fragment and the substituent at the pyrrole nitrogen. This general motif of an oxidized decalin linked to a heterocyclic moiety by an ethylene bridge is also found in other natural products such as vitexlactam A,[2] marrubiin[3-5] and vitetrifolin H.[6] Vitepyrroloid A displayed cytotoxic activity against a human nasopharyngeal carcinoma cell line (CNE1) with an IC_{50} value of 8.7 µM. Deeper explorations of its biomedical potential were inhibited by a low isolation yield of $3 \cdot 10^{-5}$ %. Therefore, the development of an efficient chemical synthesis of vitepyrroloid A would allow for further biological studies.

When contemplating potential synthetic approaches, we opted for a late-stage sp^2-sp^3 coupling between C12 and C13. Such a disconnection might be applicable not only to the synthesis of vitepyrroloid A but also enable the synthesis of the other natural products shown in Figure 1. Among possible coupling reactions, we favored a cross-electrophile coupling over the Suzuki-Miyaura coupling as an alkyl halide appeared more readily accessible than a corresponding borane. As shown in our retrosynthetic analysis (Figure 2), vitepyrroloid A (**1**) can be disconnected into 3-bromopyrrole **4** and alkyl iodide **5**. The pyrrole coupling partner **4** is accessible from the commercially available pyrrole derivative **6**. For the synthesis of the decalin coupling partner **5**, we identified the terpenoid (+)-sclareolide as potential starting material[7-11] in accordance with long-standing interest in the utilization of terpene feedstock as suitable building blocks,[12-14] thus minimizing the number of C-C-bond forming reactions.

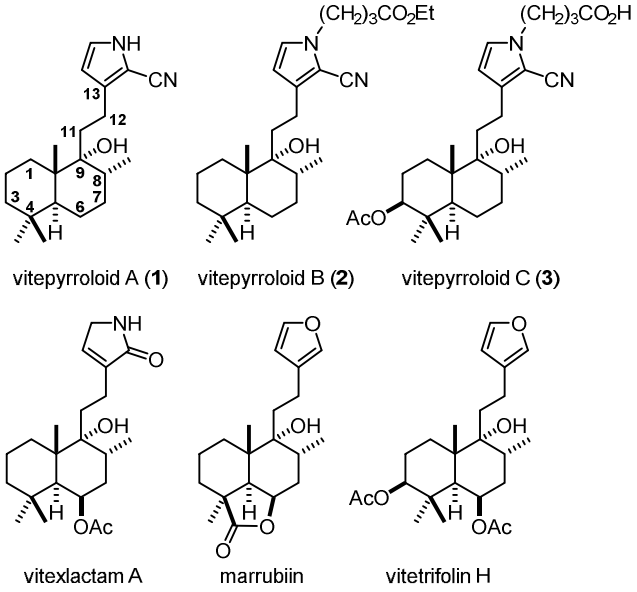


Figure 1. Structures of vitepyrroloids A-C (**1**-**3**), vitexlactam A, marrubiin, and vitetrifolin H.

Concerning the modification of sclareolide, the challenge lies in realizing a 1,2-transposition of the C8 oxygen to C9 that

controls the configurations of the two affected stereogenic centers.

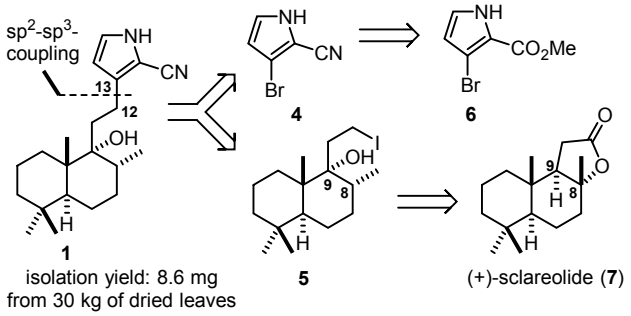
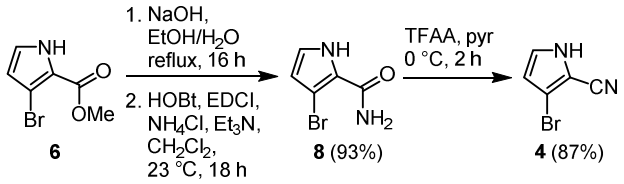


Figure 2. Retrosynthetic analysis.

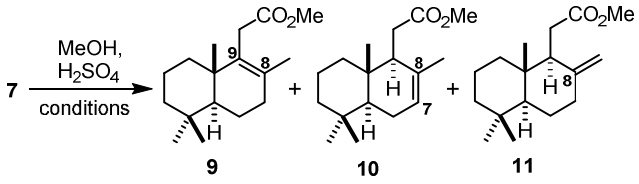
The synthesis of bromopyrrole **4** commenced with the basic hydrolysis of the commercially available methyl ester **6**[15] followed by formation of amide **8** using HOBt as activating agent and ammonium chloride as nitrogen source (Scheme 1). Subsequently, the amide **8** was dehydrated to nitrile **4** in 87% yield using TFAA in pyridine.

Scheme 1. Synthesis of bromopyrrole **4**.



The synthesis of the decalin fragment started from commercially available (+)-sclareolide (**7**). Treatment with sulfuric acid in methanol[16] resulted in the methanolysis of the lactone and elimination of the resulting tertiary alcohol at C8. The ratio of $\Delta^{8,9}$-alkene **9**, $\Delta^{7,8}$-alkene **10**, and the exocyclic alkene isomer **11** is strongly dependent on the reaction temperature and reaction time (Table 1). At 23 °C, the reaction was complete after 3 days to afford a mixture of alkenes **9**–**11**, with the $\Delta^{7,8}$-alkene **10** as the major product (entry 1).

Table 1. Methanolysis/Elimination of (+)-sclareolide (**7**).

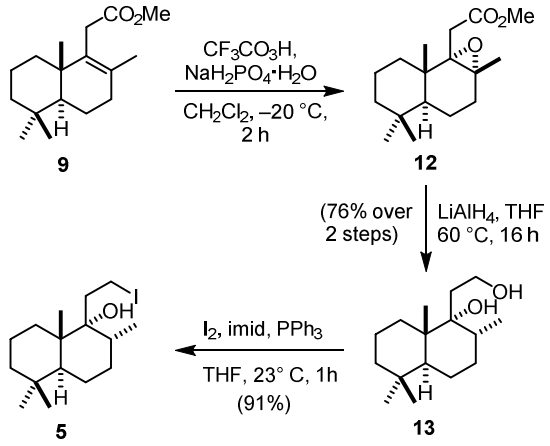


entry	T [°C]	t [d]	**9** [%][a]	**10** [%][a]	**11** [%][a]
1	23	3	9	53	38
2	65	1	49	51	-
3	**65**	**5**	**70**	**30**	**-**
4[b]	95	7	68	32	-

[a]Isolated yields are displayed. [b]The reaction was carried out in a pressure tube.

Raising the temperature to 65 °C resulted after 1 day in the formation of roughly equal amounts of the alkenes **9** and **10** (entry 2). Equilibration of the reaction mixture at 65 °C for 5 days (entry 3) afforded the desired $\Delta^{8,9}$-isomer **9** as the major product in 70% yield along with 30% of alkene **10**. A further increase of the reaction time or performing the reaction in a pressure tube at 95 °C bath temperature (entry 4) did not change isomeric ratios. After separation of **9** and **10** by column chromatography, alkene **9** was epoxidized with in situ generated trifluoroperoxyacetic acid (Scheme 2) to give **12** as an inseparable 16:1 mixture of diastereomers. Reduction of the ester and concomitant reductive opening[10] of the epoxide moiety with $LiAlH_4$ afforded diol **13** which was isolated as single diastereomer in 76% yield. Finally, the terminal hydroxyl group was converted to an iodide with I_2/PPh_3/imidazole[17] to give **5** in 91% yield.

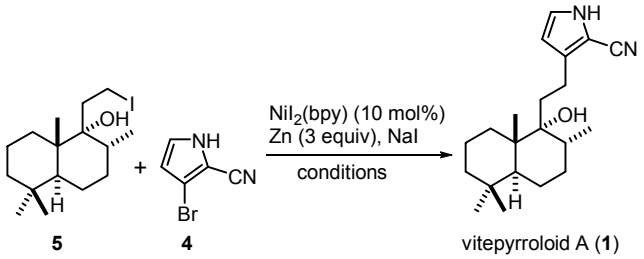
Scheme 2. Synthesis of alkyl iodide **5**.



With the two functionalized building blocks **4** and **5** in hand, a conservative coupling strategy might involve conversion of alkyl iodide **5** into a nucleophilic coupling partner e.g. via halogen-metal-exchange or elimination/hydroboration. In order to avoid additional steps and the use of protecting groups, a direct coupling reaction was sought that would tolerate the functional groups present. Cross-electrophile couplings have witnessed a tremendous evolution in over the last two decades.[18-20] Yet, they are far from being a standard transformation in the synthesis of natural products.[21] Potential obstacles include reductive homocoupling, hydride functionalization and catalyst deactivation. The application of literature-reported catalytic systems such as $NiCl_2$/phen,[22] $CoBr_2$/P(*p*-Tol)$_3$,[23] $PdCl_2$/amphos[24] or NiI_2(dme)[25] did not yield any desired product. With the dual ligand $NiI_2 \cdot H_2O$-system,[26] only traces of the desired product could be detected. Eventually, a system developed by Qian and Gong,[27] NiI_2/bpy in dimethylacetamide (DMAc) with 3 equiv of Zn as reductant, afforded vitepyrroloid A (**1**) in 12% yield (Table 2, entry 1). The use of NaI (2 equiv) as additive increased the yield to 24% (entries 2,3). Weix[19] suggested that NaI suppresses the formation of homocoupling products. Raising the temperature from 50 to 70 °C further improved the yield to 40% (entry 4). Changing the solvent to NMP and 1,4-dioxane led to a decreased yield (entries 5,6) while DMF and DMPU inhibited the reaction. When two equivalents of the alkyl iodide **5** were used, vitepyrroloid A (**1**) was isolated in 57% yield (entry 7). Manganese or B_2pin_2[28] as reducing agents and other ligands than bpy did not provide beneficial effects in either case. Under electrochemi-

cal conditions,[29] the product was formed in 21% yield (see Supporting Information for additional screening results).

Table 2. Cross-electrophile coupling of **4** and **5**.[a]



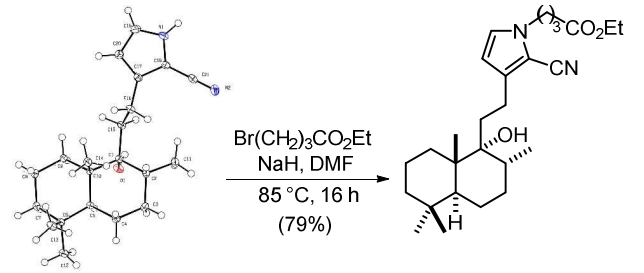
5 **4** vitepyrroloid A (**1**)

entry	NaI [equiv]	solvent	temp [°C]	**1** [%]
1	0	DMAc	50	12
2	1	DMAc	50	19
3	2	DMAc	50	24
4	2	DMAc	70	40
5	2	NMP	70	31
6	2	1,4-dioxane	70	16
7[b]	**2**	**DMAc**	**70**	**57**

[a]Reaction conditions: **4** (1.0 equiv), **5** (1.0 equiv), NiI_2(bpy) (10 mol%), Zn (3.0 equiv), solvent (0.16 M). [b] 2.0 equiv of alkyl iodide **5** were used.

The reported absolute configuration of **1** was confirmed by X-ray diffraction. Moreover, it was possible to convert vitepyrroloid A (**1**) into vitepyrroloid B (**2**) by *N*-alkylation with ethyl 4-bromobutyrate using sodium hydride in DMF (Scheme 3).

Scheme 3. Synthesis of Vitepyrroloid B (**2**) from **1** (displacement ellipsoids are drawn at 50% probability level).



ORTEP of **1** vitepyrroloid B (**2**)

In summary, the first synthesis of vitepyrroloids A and B has been achieved in five and six steps respectively, from commercially available starting materials. The application of a cross-electrophile coupling strategy was key to rendering the overall sequence concise and protecting-group-free. With a reliable access to vitepyrroloid A and its congeners, we are now in a position to investigate their biological activity.

EXPERIMENTAL SECTION

General Information. All reactions sensitive to moisture and/or air were performed under an argon atmosphere using Schlenk techniques. Reagents and solvents were obtained from commercial sources and used as received unless otherwise noted. NiI_2(bpy) and analogs were prepared according to literature.[30] Nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were recorded at the following frequencies: ^{1}H NMR at 500 and 700 MHz, ^{13}C NMR at 125 and 175 MHz with solvent resonance as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 and DMSO-*d*6 at 2.50 , ^{13}C NMR: $CDCl_3$ at 77.0 and DMSO-*d*6 at 39.5). ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet), coupling constant (Hz), and integration. High resolution mass spectra were measured with a TOF mass spectrometer. TLC visualization was accomplished using UV light, Cer(IV)-sulfate solution in water, or acidic *p*-anisaldehyde solution in ethanol. Yields refer to isolated yields after flash column chromatography.

*3-Bromo-1H-pyrrole-2-carboxamide (**8**).* To a solution of methyl ester **6** (467 mg, 2.29 mmol, 1.0 equiv) in EtOH/H_2O (1:1 v/v; 22.9 mL) was added NaOH (183 mg, 4.58 mmol, 2.0 equiv), and the mixture was heated to reflux for 16 h. Upon concentration under reduced pressure, the residue was dissolved in EtOAc (50 mL) and successively washed with 1M HCl (10 mL) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude carboxylic acid was dissolved in anhydrous CH_2Cl_2 (7.0 mL) and HOBt (351 mg, 2.60 mmol, 1.2 equiv), and EDCl (499 mg, 2.60 mmol, 1.2 equiv) were added subsequently. The mixture was stirred for 10 min at 23 °C before NH_4Cl (173 mg, 3.23 mmol, 1.49 equiv) and NEt_3 (0.45 mL, 3.26 mmol, 1.5 equiv) were added. The reaction was stirred for 18 h and then quenched by the addition of H_2O (10 mL). After extraction with EtOAc (3 x 25 mL), the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. After purification by column chromatography (*n*-pentane/EtOAc = 1:1) amide **8** (400 mg, 2.12 mmol, 98%) was obtained as a colorless solid. R_f = 0.30 (*n*-pentane/EtOAc = 1:1); mp = 175–176 °C; IR: $\tilde{\nu}$ = 3458, 3298, 3161, 3133, 1640, 1590, 1461, 1443, 1425, 987, 729 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d6): δ = 11.81 (brs, 1H), 7.43 (brs, 1H), 7.03 – 6.88 (m, 1H), 6.81 (brs, 1H), 6.24 (t, J = 2.7 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d6): δ = 160.8, 123.0, 121.9, 112.5, 97.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_5H_5BrN_2OH$ 188.9658, found 188.9658; $[M+Na]^+$ calculated for $C_5H_5BrN_2ONa$ 210.9477, found 210.9476.

*3-Bromo-1H-pyrrole-2-carbonitrile (**4**).* Amide **8** (212 mg, 1.12 mmol, 1.0 equiv) was dissolved in pyridine (5.7 mL), and TFAA (0.63 mL, 4.48 mmol, 4.0 equiv) was added dropwise at 0 °C. The reaction mixture was stirred at this temperature for 2 h, then diluted with EtOAc (60 mL) and washed with saturated $NaHCO_3$ solution, 1M HCl and brine. The organic phase was dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/EtOAc = 3:1) to give the nitrile **4** (166 mg, 0.971 mmol, 87%) as a colorless solid. R_f = 0.30 (*n*-pentane/EtOAc = 5:1); mp = 95–96 °C; IR: $\tilde{\nu}$ = 3321, 3145, 2217, 1426, 1388, 1001, 746 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$): δ = 9.67 (brs, 1H), 6.90 (t, J = 3.0 Hz, 1H), 6.33 (t, J = 2.7 Hz, 1H); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 124.7, 113.3, 113.2, 108.7, 102.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calculated for $C_5H_3BrN_2H$ 170.9553, found 170.9550; $[M+Na]^+$ calculated for $C_5H_3BrN_2Na$ 192.9372, found 192.9367.

*Methyl 2-((8aS)-2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)acetate (**9**).*[31,32] To a solution of (+)-sclareolide **7** (1.00 g, 4.00 mmol) in MeOH (19 mL), was added conc. H_2SO_4 (0.7 mL) and the mixture heated to reflux for

5 days. MeOH was distilled off and the residue was dissolved in Et_2O (100 mL), washed with H_2O, saturated $NaHCO_3$ solution, and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude alkene mixture was separated by column chromatography (*n*-pentane/Et_2O = 120:1 to 80:1) to give alkenes $\Delta^{8,9}$- **9** (740 mg, 2.80 mmol, 70%) and Δ^{7}-**10** (317 mg, 1.20 mmol, 30%) as colorless oils. **9**: R_f = 0.46 (*n*-pentane/Et_2O = 40:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.66 (s, 3H), 3.08 (d, *J* = 16.8 Hz, 1H), 2.97 (d, *J* = 17.0 Hz, 1H), 2.11 (dd, *J* = 11.5, 6.8 Hz, 1H), 2.02 (dd, *J* = 17.9, 6.4 Hz, 1H), 1.72 – 1.62 (m, 2H), 1.61 – 1.57 (m, 1H), 1.56 (s, 6H), 1.49 – 1.34 (m, 3H), 1.21 (dd, *J* = 12.7, 1.9 Hz, 1H), 1.19 – 1.07 (m, 2H), 0.92 (s, 6H), 0.88 (s, 6H), 0.83 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.6, 134.0, 130.4, 51.8, 51.5, 41.7, 38.7, 36.4, 33.8, 33.4, 33.3, 33.0, 21.8, 20.2, 19.9, 19.1 (2C). **10:** R_f = 0.47 (*n*-pentane/Et_2O = 40:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.47 – 5.39 (m, 1H), 3.68 (s, 3H), 2.49 (d, *J* = 9.5 Hz, 1H), 2.42 – 2.35 (m, 1H), 2.17 (dd, *J* = 16.5, 9.7 Hz, 1H), 2.04 – 1.95 (m, 1H), 1.84 (dddt, *J* = 17.5, 12.0, 4.5, 2.4 Hz, 1H), 1.75 – 1.65 (m, 1H), 1.56 – 1.53 (m, 3H), 1.53 – 1.37 (m, 3H), 1.28 (dd, *J* = 12.2, 4.7 Hz, 1H), 1.18 (td, *J* = 13.1, 3.6 Hz, 1H), 1.09 (td, *J* = 13.0, 3.9 Hz, 1H), 0.88 (s, 3H), 0.86 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5, 133.8, 122.9, 51.9, 50.7, 49.9, 42.2, 39.2, 36.1 33.3, 33.1, 23.8, 22.0, 21.5, 18.9, 14.1 (2C).

*Methyl 2-((1aR,7aS,7bS)-1a,4,4,7a-tetramethyloctahdronaphtho[1,2-b]oxiren-7b(1aH)-yl)acetate **(12)***. TFAA (0.21 mL, 1.51 mmol, 2.0 equiv) was added dropwise to a suspension of UHP (156 mg, 1.66 mmol, 2.2 equiv) in MeCN (4.6 mL) at 0 °C. The resulting solution was stirred for 45 min and then added to a suspension of alkene **9** (200 mg, 0.756 mmol, 1.0 equiv) and $NaH_2PO_4{\cdot}2H_2O$ (538 mg, 3.02 mmol, 4.0 equiv) in CH_2Cl_2 (9.2 mL) at –20 °C. The mixture was stirred for 2 h at this temperature, then diluted with H_2O (10 mL) and extracted with Et_2O (4 x 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. After purification by column chromatography (*n*-pentane/Et_2O = 8:1) the epoxide **12** (193 mg, 0.688 mmol, 86%, d.r. = 16:1, in total 91%) was obtained as colorless oil. R_f = 0.36 (*n*-pentane/Et_2O = 8:1); IR: $\tilde{\nu}$ = 2946, 2924, 1741, 1457, 1434, 1380, 1333, 1266, 1194, 1161 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.65 (s, 3H), 2.84 (d, *J* = 15.9 Hz, 1H), 2.50 (d, *J* = 15.9 Hz, 1H), 1.96 – 1.79 (m, 2H), 1.74 – 1.66 (m, 1H), 1.54 – 1.48 (m, 2H), 1.45 (dd, *J* = 12.9, 2.4 Hz, 1H), 1.40 – 1.32 (m, 3H), 1.29 (s, 3H), 1.27 – 1.20 (m, 1H), 1.15 (td, *J* = 12.7, 5.2 Hz, 1H), 0.97 (s, 3H), 0.82 (s, 3H), 0.78 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 69.8, 63.7, 52.0, 43.1, 41.6, 38.9, 35.00, 34.9, 34.0, 33.3, 29.8, 22.7, 21.8, 18.8, 17.6, 17.3; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{17}H_{28}O_3Na$ 303.1930, found 303.1937.

*(1R,2R,8aS)-1-(2-Hydroxyethyl)-2,5,5,8a-tetramethyldecahydronaphthalen-1-ol **(13)***. $LiAlH_4$ (118 mg, 3.11 mmol, 5.5 equiv) was suspended in anhydrous THF (2.2 mL) and a solution of epoxide **12** (159 mg, 0.567 mmol, d.r. = 16:1, 1.0 equiv) in anhydrous THF (10 mL) was added dropwise. The mixture was heated to 60 °C and stirred at this temperature for 16 h. After cooling to 23 °C, the reaction was quenched by the careful addition of EtOAc (10 mL) and 1M HCl (10 mL). The reaction mixture was extracted with EtOAc (4 x 30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Diol **13** (117 mg, 0.460 mmol, 81%, 76% over two steps) was obtained as a colorless solid after column chromatography (*n*-pentane/EtOAc = 5:1). R_f = 0.42 (*n*-pentane/EtOAc = 5:1); mp = 76–77 °C; $[\alpha]_D^{24}$ = +16.6 ($CHCl_3$, c = 1.0); IR: $\tilde{\nu}$ = 3336, 2963, 2933, 2870, 1455, 1386, 1362, 1133, 1046, 1038, 720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (td, *J* = 10.7, 2.7 Hz, 1H), 3.72 (dt, *J* = 9.9, 4.3 Hz, 1H), 2.48 (brs, 1H), 2.34 (brs, 1H), 2.04 (ddd, *J* = 15.2, 9.5, 3.9 Hz, 1H), 1.74 – 1.66 (m, 1H), 1.58 – 1.43 (m, 7H), 1.38 – 1.19 (m, 4H), 1.15 (td, *J* = 13.5, 3.9 Hz, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 78.5, 61.6, 46.3, 43.2, 41.9, 37.7, 35.5, 33.8, 33.5, 31.8, 31.3, 22.0, 21.6, 18.7, 16.4, 15.9; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{16}H_{30}O_2Na$ 277.2138, found 277.2152.

*(1R,2R,8aS)-1-(2-Iodoethyl)-2,5,5,8a-tetramethyldecahydronaphthalen-1-ol **(5)***. To a solution of **13** (136 mg, 0.535 mmol, 1.0 equiv) in anhydrous THF (11 mL) was added PPh_3 (154 mg, 0.588 mmol, 1.1 equiv), imidazole (73.0 mg, 1.07 mmol, 2.0 equiv), and I_2 (149 mg, 0.588 mmol, 1.1 equiv), and the mixture stirred for 1 h at 23 °C. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ solution (20 mL), extracted with Et_2O (3 x 30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (*n*-pentane/Et_2O = 30:1) giving the iodide **5** (177 mg, 0.485 mmol, 91%) as a colorless solid.

R_f = 0.61 (*n*-pentane/Et_2O = 30:1); mp = 45–47 °C; $[\alpha]_D^{25}$ = +26.9 ($CHCl_3$, c = 1.0); IR: $\tilde{\nu}$ = 3594, 2937, 2896, 2867, 1458, 1384, 1319, 1171, 958 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.31 – 3.13 (m, 2H), 2.34 (ddd, *J* = 14.6, 11.8, 6.4 Hz, 1H), 2.04 (ddd, *J* = 14.6, 11.4, 5.6 Hz, 1H), 1.74 (dqd, *J* = 13.2, 6.6, 4.1 Hz, 1H), 1.60 – 1.47 (m, 4H), 1.47 – 1.41 (m, 1H), 1.36 (dt, *J* = 12.1, 2.9 Hz, 1H), 1.32 – 1.28 (m, 2H), 1.28 – 1.18 (m, 2H), 1.18 – 1.07 (m, 1H), 0.90 (s, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 79.1, 46.5, 43.2, 41.8, 40.4, 37.0, 33.8, 33.5, 32.0, 31.1, 22.1, 21.6, 18.6, 16.5, 16.1, 4.1; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{16}H_{29}IONa$ 387.1155, found 387.1156.

General Procedure for Cross-Electrophile Coupling. *Example for entry 7. (+)-Vitepyrroloid A **(1)***. Iodide **5** (35.0 mg, 0.0960 mmol, 2.0 equiv), nitrile **4** (8.20 mg, 0.0480 mmol, 1.0 equiv), Zn (9.40 mg, 0.144 mmol, 3.0 equiv), NaI (14.4 mg, 0.0960 mmol, 2.0 equiv) and NiI_2(bpy) (2.20 mg, 0.600 µmol, 10 mol%) were placed in a Schlenk flask under an argon atmosphere and the flask evacuated and flashed with argon (3 x). Afterwards, anhydrous DMAc (0.3 mL) was added and the brown mixture was stirred for 16 h at 70 °C. The mixture was diluted with H_2O (5.0 mL) and the resulting black solution was extracted with EtOAc (4 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. (+)-Vitepyrroloid A was obtained after column chromatography (*n*-pentane/EtOAc = 6.5:1) and subsequent recrystallization (MeOH) as a colorless solid (9.00 mg, 0.0274 mmol, 57%).

R_f = 0.31 (*n*-pentane/EtOAc = 5:1); mp = 158–160 °C; $[\alpha]_D^{25}$ = +8.64 (MeOH, c = 0.87), Lit.[1]: $[\alpha]_D^{25}$ = +10 (MeOH, c = 0.2); IR: $\tilde{\nu}$ = 3599, 3344, 2933, 2916, 2863, 2209, 1457, 1444, 1405, 1382, 1258, 1133, 759 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$): δ = 8.48 (brs, 1H) 6.84 (t, *J* = 2.9 Hz, 1H), 6.14 (t, *J* = 2.7 Hz, 1H), 2.67 (ddd, *J* = 21.2, 12.0, 5.7 Hz, 2H), 1.94 (ddd, *J* = 14.4, 12.2, 6.0 Hz, 1H), 1.84 – 1.81 (m, 1H), 1.73 – 1.68 (m, 1H), 1.60 – 1.48 (m, 6H), 1.42 (dd, *J* = 12.0, 2.6 Hz, 1H), 1.38 – 1.34 (m, 1H), 1.33 – 1.24 (m, 2H), 1.16 (td, *J* = 13.2,

3.5 Hz, 1H), 0.96 (d, J = 6.7 Hz, 3H), 0.95 (s, 3H), 0.88 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 138.0, 123.2, 114.2, 110.0, 99.2, 77.0, 46.4, 43.3, 41.7, 36.6, 35.7, 33.8, 33.4, 31.9, 31.3, 23.3, 22.0, 21.6, 18.6, 16.4, 16.2; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{21}H_{32}N_2ONa$ 351.2407, found 351.2402; $[M+K]^+$ calculated for $C_{21}H_{32}N_2OK$ 367.2147, found 367.2164.

(+)-Vitepyrroloid B (2). (+)-Vitepyrroloid A (8.0 mg, 24 µmol, 1.0 equiv) dissolved in anhydrous DMF (0.7 mL) was treated with NaH (1.3 mg, 32 µmol, 60 w% 1.3 equiv). The solution was stirred for 20 min at 23 °C before ethyl 4-bromobutyrate (4.50 µL, 32 µmol, 1.3 equiv) was added and stirring was continued for 16 h at 85 °C. The mixture was diluted with H_2O (3.0 mL) and the resulting yellow solution was extracted with EtOAc (4 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. (+)-Vitepyrroloid B (8.0 mg, 19 µmol, 79%) was obtained after column chromatography (*n*-pentane/EtOAc = 5:1).
R_f = 0.34 (*n*-pentane/EtOAc = 5:1); $[\alpha]_D^{23}$ = +9.8 (MeOH, c = 0.70), Lit.[1]: $[\alpha]_D^{25}$ = +9 (MeOH, c = 0.2); IR: $\tilde{\nu}$ = 3510, 2933, 2868, 2209, 1458, 1444, 1408, 1374, 1239, 1182, 1024, 738, 651 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.72 (d, J = 2.5 Hz, 1H), 6.02 (d, J = 2.4 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.04 (t, J = 6.9 Hz, 2H), 2.80 – 2.52 (m, 2H), 2.28 (t, J = 7.2 Hz, 2H), 2.11 (p, J = 7.0 Hz, 2H), 1.96 – 1.86 (m, 1H), 1.84 – 1.78 (m, 1H), 1.73 – 1.65 (m, 1H), 1.62 – 1.40 (m, 8H), 1.37 – 1.29 (m, 3H), 1.28 – 1.24 (t, J = 7.2 Hz, 3H), 1.15 (td, J = 13.1, 3.4 Hz, 1H), 0.96 (d, J = 7.2 Hz, 3H), 0.94 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.8, 138.5, 126.7, 114.2, 109.6, 102.3, 77.4, 61.1, 48.2, 46.8, 43.6, 42.1, 37.0, 36.1, 34.1, 33.7, 32.2, 31.7, 31.2, 26.6, 24.0, 22.4, 22.0, 19.0, 16.8, 16.6, 14.6; HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calculated for $C_{27}H_{42}N_2O_3Na$ 465.3087, found 465.3101; $[M+K]^+$ calculated for $C_{27}H_{42}N_2O_3K$ 481.2851, found 481.2841.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Screening, spectroscopic, and X-ray crystallography data (PDF)

Accession Codes

CCDC 1819079 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

* E-mail: mathias.christmann@fu-berlin.de

ORCID

Mathias Christmann: 0000-0001-9313-2392

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Luo, P.; Xia, W.; Morris-Natschke, S. L.; Lee, K.-H.; Zhao, Y.; Gu, Q.; Xu, J. Vitepyrroloids A–D, 2-Cyanopyrrole-Containing Labdane Diterpenoid Alkaloids from the Leaves of Vitex trifolia. *J. Nat. Prod.* **2017**, *80*, 1679–1683.
(2) Li, S.-H.; Zhang, H.-J.; Qiu, S.-X.; Niu, X.-M.; Santarsiero, B. D.; Mesecar, A. D.; Fong, H. H. S.; Farnsworth, N. R.; Sun, H.-D. Vitexlactam A, a novel labdane diterpene lactam from the fruits of Vitex agnus-castus. *Tetrahedron Lett.* **2002**, *43*, 5131–5134.
(3) Mangoni, L.; Adinolfi, M.; Laonigro, G.; Caputo, R. Synthesis of marrubiin. *Tetrahedron* **1972**, *28*, 611–621.
(4) Yamakoshi, H.; Sawayama, Y.; Akahori, Y.; Kato, M.; Nakamura, S. Total Syntheses of (+)-Marrubiin and (−)-Marrulibacetal. *Org. Lett.* **2016**, *18*, 3430–3433.
(5) Popoola, O.; Elbagory, A.; Ameer, F.; Hussein, A. Marrubiin. *Molecules* **2013**, *18*, 9049–9060.
(6) Wu, J.; Zhou, T.; Zhang, S.-w.; Zhang, X.-h.; Xuan, L.-j. Cytotoxic Terpenoids from the Fruits of Vitex trifolia L. *Planta Med.* **2009**, *75*, 367–370.
(7) Kumar, C. N. S. S. P.; Chein, R.-J. Synthesis of Labdane Diterpenes Galanal A and B from (+)-Sclareolide. *Org. Lett.* **2014**, *16*, 2990–2992.
(8) Wei, Z.; Hongliang, Y.; Jingxun, Y.; Zhihong, Z.; Rongbiao, T. Total Syntheses of Sesterterpenoid Ansellones A and B, and Phorbadione. *Angew. Chem. Int. Ed.* **2017**, *56*, 4787–4791.
(9) Dixon, D. D.; Lockner, J. W.; Zhou, Q.; Baran, P. S. Scalable, Divergent Synthesis of Meroterpenoids via "Borono-sclareolide". *J. Am. Chem. Soc.* **2012**, *134*, 8432–8435.
(10) George, J. H.; Baldwin, J. E.; Adlington, R. M. Enantiospecific, Biosynthetically Inspired Formal Total Synthesis of (+)-Liphagal. *Org. Lett.* **2010**, *12*, 2394–2397.
(11) George, J. H.; McArdle, M.; Baldwin, J. E.; Adlington, R. M. Biomimetic rearrangements of simplified labdane diterpenoids. *Tetrahedron* **2010**, *66*, 6321–6330.
(12) Bartels, F.; Hong, Y. J.; Ueda, D.; Weber, M.; Sato, T.; Tantillo, D. J.; Christmann, M. Bioinspired synthesis of pentacyclic onocerane triterpenoids. *Chemical Science* **2017**, *8*, 8285–8290.
(13) Winter, P.; Vaxelaire, C.; Heinz, C.; Christmann, M. Transforming terpene feedstock into polyketide architecture. *Chem. Commun.* **2011**, *47*, 394–396.
(14) Winter, P.; Swatschek, J.; Willot, M.; Radtke, L.; Olbrisch, T.; Schafer, A.; Christmann, M. Transforming terpene-derived aldehydes into 1,2-epoxides via asymmetric [small alpha]-chlorination: subsequent epoxide opening with carbon nucleophiles. *Chem. Commun.* **2011**, *47*, 12200–12202.
(15) Hasse, K.; Willis, A. C.; Banwell, M. G. A Total Synthesis of the Marine Alkaloid Ningalin B from (S)-Proline. *Aust. J. Chem.* **2009**, *62*, 683–691.

(16) Koltsa, M. N.; Mironov, G. N.; Vlad, P. F. Synthesis of (+)-drim-8-en-11-oic acid. *Chem. Nat. Compd.* **1991**, *27*, 183–188.
(17) Garegg, P. J.; Samuelsson, B. Novel reagent system for converting a hydroxy-group into an iodo-group in carbohydrates with inversion of configuration. *J. Chem. Soc., Chem. Commun.* **1979**, 978–980.
(18) Durandetti, M.; Nédélec, J.-Y.; Périchon, J. Nickel-Catalyzed Direct Electrochemical Cross-Coupling between Aryl Halides and Activated Alkyl Halides. *J. Org. Chem.* **1996**, *61*, 1748–1755.
(19) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146– 6159.
(20) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. Reductive Cross-Coupling Reactions between Two Electrophiles. *Chem. Eur. J.* **2014**, *20*, 6828– 6842.
(21) Fegheh-Hassanpour, Y.; Arif, T.; Sintim, H. O.; Al Mamari, H. H.; Hodgson, D. M. Synthesis of (−)-6,7-Dideoxysqualestatin H5 by Carbonyl Ylide Cycloaddition–Rearrangement and Cross-electrophile Coupling. *Org. Lett.* **2017**, *19*, 3540–3543.
(22) Cai, D.-J.; Lin, P.-H.; Liu, C.-Y. Cobalt-Catalyzed Reductive Alkylation of Heteroaryl Bromides: One-Pot Access to Alkylthiophenes, -furans, -selenophenes, and -pyrroles. *Eur. J. Org. Chem.* **2015**, 5448–5452.
(23) Lu, X.; Yi, J.; Zhang, Z.-Q.; Dai, J.-J.; Liu, J.-H.; Xiao, B.; Fu, Y.; Liu, L. Expedient Synthesis of Chiral α-Amino Acids through Nickel-Catalyzed Reductive Cross-Coupling. *Chem. Eur. J.* **2014**, *20*, 15339–15343.
(24) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. Zn-Mediated, Pd-Catalyzed Cross-Couplings in Water at Room Temperature Without Prior Formation of Organozinc Reagents. *J. Am. Chem. Soc.* **2009**, *131*, 15592–15593.
(25) Hansen, E. C.; Li, C.; Yang, S.; Pedro, D.; Weix, D. J. Coupling of Challenging Heteroaryl Halides with Alkyl Halides via Nickel-Catalyzed Cross-Electrophile Coupling. *J. Org. Chem.* **2017**, *82*, 7085–7092.
(26) Everson, D. A.; Shrestha, R.; Weix, D. J. Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2010**, *132*, 920–921.
(27) Xue, W.; Xu, H.; Liang, Z.; Qian, Q.; Gong, H. Nickel-Catalyzed Reductive Cyclization of Alkyl Dihalides. *Org. Lett.* **2014**, *16*, 4984–4987.
(28) Zhang, G.; Xie, Y.; Wang, Z.; Liu, Y.; Huang, H. Diboron as a reductant for nickel-catalyzed reductive coupling: rational design and mechanistic studies. *Chem. Commun.* **2015**, *51*, 1850–1853.
(29) Perkins, R. J.; Pedro, D. J.; Hansen, E. C. Electrochemical Nickel Catalysis for Sp2-Sp3 Cross-Electrophile Coupling Reactions of Unactivated Alkyl Halides. *Org. Lett.* **2017**, *19*, 3755–3758.
(30) Johnson, K. A.; Biswas, S.; Weix, D. J. Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides. *Chem. Eur. J.* **2016**, *22*, 7399–7402.
(31) Carman, R. W.; Deeth, H. C. Diterpenoids. XXVIII. The synthesis of α-onoceradiene from abienol. *Aust. J. Chem.* **1971**, *24*, 1099–1102.
(32) Bendall, J. G.; Cambie, R. C.; Moratti, S. C.; Riutledge, P. S.; Woodgate, P. D. Synthesis of a Novel Diterpenoid Rearrangement Product. *Aust. J. Chem.* **1995**, *48*, 1747–1755.