VIP Natural Products

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Total Synthesis of (+)-Daphmanidin E**

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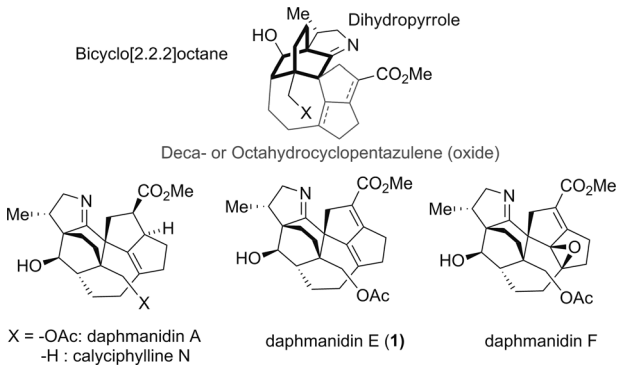
The daphniphyllum alkaloids have inspired organic chemists to devise novel strategies and to develop tailored methods aimed at synthesizing these complex structures.[1,2] The daphmanidins constitute a recent addition to this structurally diverse class of alkaloids isolated from *Daphniphyllaceae*. These can be further categorized into two skeletal types, namely type A (hexacyclic) and type C (pentacyclic).[1] The characteristic feature of the A-type alkaloids is an unprecedented hexacyclic structure, which includes a fused dihydropyrrole along with an embedded deca- or octahydrocyclopentazulene (oxide) around a central bicyclo[2.2.2]octane (Scheme 1).

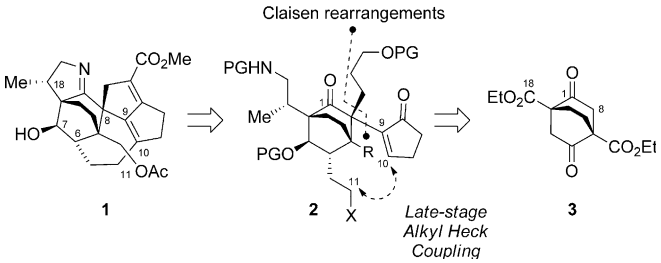


Scheme 1. Type A daphmanidin alkaloids.

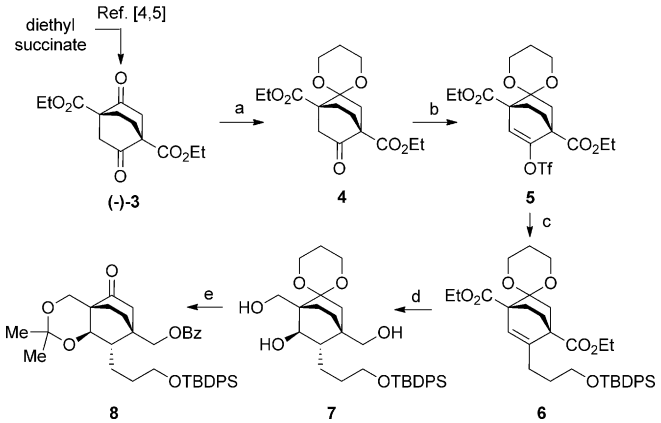
Herein, we describe the successful total synthesis of (+)-daphmanidin E, which is also the first synthesis of a type A daphmanidin alkaloid. The key features of the strategy involve rapid access to an enantiomerically pure bicyclo[2.2.2]octadione and elaboration around its periphery through the implementation of two Claisen rearrangements, a diastereoselective hydroboration, and a cobalt-catalyzed alkyl-Heck cyclization.

Daphmanidin E (**1**, Scheme 1) was isolated in 2006 from leaves of *Daphniphyllum teijsmannii*, and was shown to exhibit moderate vasorelaxant activity on rat aorta.[3] The complex architecture with three quaternary stereogenic centers and a central bicyclo[2.2.2]octane core constitutes a challenging target. We became attracted by the possibility of starting from the readily available building block **3**, which features two quaternary stereogenic centers and the bicyclo[2.2.2]octane skeleton with suitably functionalized bridgehead positions (Scheme 2). The C(1) ketone (daphmanidin numbering) provides a handle for the introduction of the quaternary center at C(8) through alkylation reactions or Claisen rearrangements, and one of the bridgehead carboxylate groups would provide entry to the fused dihydropyrrole. Key to the overall plan is a late-stage cyclization through an alkyl-Heck coupling to access the embedded seven-membered ring of the octahydroazulene (see **2**, Scheme 2).

The synthesis commenced with the C_2-symmetric, enantiomerically enriched bicyclo[2.2.2]octadione (−)-**3** (e.r. ≥ 95:5; Scheme 3). This compound was obtained by resolution



Scheme 2. Retrosynthetic analysis of daphmanidin E (PG = protection group).



Scheme 3. Reagents and conditions: a) 1,3-propanediol, *p*TsOH (10 mol%), PhH, reflux; then acetone, *p*TsOH (10 mol%), 50°C, 88%; b) KHMDS, 2-(NTf_2)-pyridine, THF, −40°C, 87%; c) $C_3H_5OSitBuPh_2$, 9-BBN, [$Pd_2(dba)_3$]/$CHCl_3$ (2 mol%), $AsPh_3$ (16 mol%), K_3PO_4, DMF/THF/H_2O, 45°C, 89%; d) $BH_3{\cdot}SMe_2$, THF, RT, then $NaBO_3{\cdot}4H_2O$; DIBAL, THF, −25°C, 72%; e) *p*TsOH (5 mol%), acetone, 50°C; BzCl, pyridine, DMAP (cat.), CH_2Cl_2, RT, 95% over 2 steps. *p*TsOH = *p*-toluenesulfonic acid, KHMDS = potassium hexamethyl disilazide, 9-BBN = 9-borabicyclo[3.3.1]nonane, dba = dibenzylideneacetone, Bz = benzoyl, DIBAL = iBu_2AlH, DMAP = 4-dimethylaminopyridine; Tf = trifluoromethylsulfonyl, TBDPS = *tert*-butyldiphenylsilyl.

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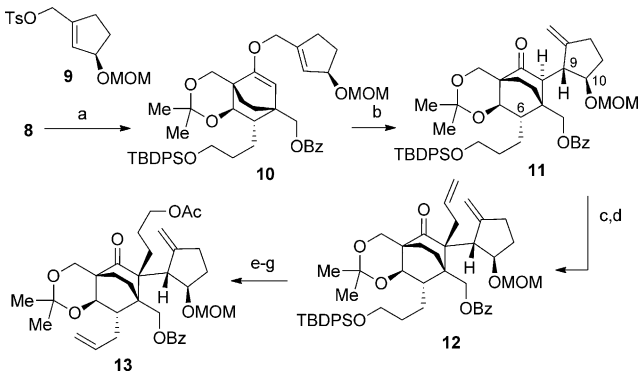
(chemoenzymatic or chromatographic separation of derived diastereomers)[4a,b] of the racemate, which is readily available in a one-pot operation from diethyl succinate.[5] The inherent C_2 symmetry of **3** renders the ketones homotopic; consequently, subsequent elaboration of **3** only necessitates operation on one ketone.[4c] Exhaustive ketalization of **3** with 1,3-propanediol followed by hydrolysis afforded monoketal **4** in 88% yield. This compound was then converted into enol triflate **5** by quenching the corresponding potassium enolate with Comins' reagent[6] (87%). *B*-alkyl Suzuki cross-coupling with the borane generated from 9-BBN and $H_2C{=}CHCH_2OTBDPS$ proceeded smoothly in the presence of $[Pd_2(dba)_3]$ (2 mol%), $AsPh_3$ (16 mol%), and K_3PO_4 in DMF at 45°C to afford **6** in excellent yield (89%).[7] The addition of $AsPh_3$ was crucial to suppress the reductive detriflation of **5** which was observed (up to 30%) when using standard phosphine ligands such as dppf (1,1′-bis(diphenylphosphanyl)ferrocene) or PPh_3.

The diastereoselective hydroboration of **6** was slow and required a high concentration ($\geq$ 1M BH_3 in THF) and excess of BH_3 to proceed at a reasonable rate.[8] Under these conditions we observed the partial reduction of the carboxylic ester at C(18). Given that the esters must ultimately undergo reduction, we decided to subject the mixture obtained after oxidative workup[9] to excess DIBAL to afford triol **7** as a single diastereoisomer (72% over 2 steps). X-ray crystallographic analysis of **7** verified the facial selectivity of the hydroboration and the correct relative configuration at C(6) and C(7).[10] The hydroxy groups were differentiated by masking the 1,3-diol as an acetonide (acetone, *p*TsOH) with concomitant hydrolysis of the 1,3-dioxane moiety. Finally, protection of the remaining primary alcohol with benzoyl chloride afforded **8** in 95% yield over 2 steps.

With ketone **8** in hand, the installation of the quaternary center at C(8) was investigated (Scheme 4). Preliminary studies indicated that O-alkylation of the enolate with allyl electrophiles was preferred under all the conditions examined. This behavior of sterically congested enolates was not unexpected,[11] and we decided to employ two consecutive Claisen rearrangements to install the quaternary center. The rearrangement was expected to occur on the sterically more accessible face of the olefin, which is differentiated by the presence of the pendant alkyl chain at C(6). Alkylation of the potassium enolate with tosylate **9** (prepared in 4 steps from (*R*)-cyclohex-2-enol, see the Supporting Information) in the presence of [18]crown-6 afforded the corresponding enol ether **10** in 89% yield. Gratifyingly, thermal rearrangement in strictly degassed nonane at 155°C afforded ketone **11** in good yield (d.r. = 10:1. 86%).[12] It is worth noting that although the stereogenic centers at C(9) and C(10) in ketone **11** are absent in the natural product, dramatic differences were observed in the behavior of the various diastereoisomers in the subsequent allylation reaction (**11**→**12**). For example, the ketone analogous to **11** but epimeric at C(10) was wholly unproductive.

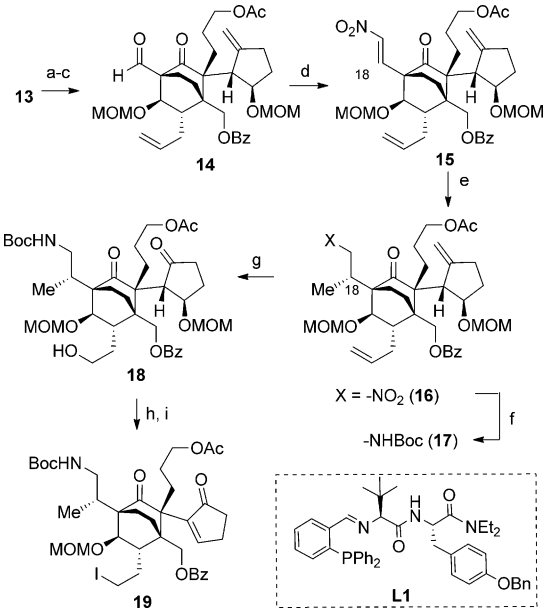


Scheme 4. Reagents and conditions: a) KHMDS, [18]crown-6, **9**, THF, −20°C, 89%; b) 155°C, nonane, d.r. = 10:1, 86%; c) KHMDS, [18]crown-6, allyl bromide, THF, −20°C, 83%; d) *o*-xylene, 165°C, 40%; e) 9-BBN, THF, RT; then $NaBO_3{\cdot}4H_2O$, 60% f) Ac_2O, pyridine, DMAP, CH_2Cl_2, RT; TBAF·3 H_2O, THF, RT, 86% g) 2-NO_2-C_6H_4SeCN, PBu_3, THF, RT; H_2O_2, pH 7 buffer, CH_2Cl_2, RT, 94%. TBAF = tetra-*n*-butyl ammonium fluoride.

Ketone **11** was subjected to allylation with KHMDS (Scheme 4), [18]crown-6, and allyl bromide to give the corresponding allyl enol ether (83%), which in turn underwent a rearrangement at 165°C in *o*-xylene to afford ketone **12** as the only isolable compound in 40% yield. The poor mass balance is caused by the formation of significant amounts of polymeric material during the reaction. Hydroboration/oxidation (9-BBN, then $NaBO_3{\cdot}4H_2O$) of the sterically more accessible olefin in **12** afforded a primary alcohol (60%), which was acetylated (Ac_2O, DMAP) and treated with TBAF to remove the TBDPS group (86% over 2 steps). Dehydration of the unveiled primary alcohol according to Grieco's protocol[13] afforded olefin **13** (94%) and set the stage for exploring ways for the installation of the stereogenic center at C(18) and generation of a suitable precursor for the amine found in daphmanidin E.

Extensive experimentation on model systems revealed that conjugate addition of a methyl carbanion to a nitroalkene **15** would constitute a viable way to install the stereogenic center at C(18) (Scheme 5). The required nitroalkene **15** was accessed by hydrolysis of the acetonide in **13** ($CeCl_3{\cdot}x\,H_2O$, oxalic acid, 98%),[14] differentiation of the primary and secondary alcohols (90% overall yield),[15] and oxidation to form aldehyde **14** (DMP, 99%).[16] A subsequent Henry condensation of **14** with nitromethane was found to be surprisingly difficult, but could be brought about by heating **14** in the presence of NH_4OAc in $MeNO_2$ (75%).[17] Most of the established procedures failed to induce dehydration of the Henry adduct to **15**. Model studies showed that when nitroalkenes similar to **15** were subjected to $ZnMe_2$/CuCN·-$(LiCl)_2$ or other reagent combinations,[18] addition products were routinely formed as a mixture of isomers (3:1–1:9) in favor of the undesired epimer. The inherent preference of the substrate for the undesired diastereomer at C(18) could be overridden by external reagent/catalyst control. Treatment of **15** with Me_2Zn and 20 mol% of the catalyst generated in situ from $[Cu(OTf)]_2$·toluene and **L1**[19] in toluene at −30–0°C afforded **16** in 90% yield as a 5:1 mixture of epimers, as determined by ^1H NMR spectroscopy.

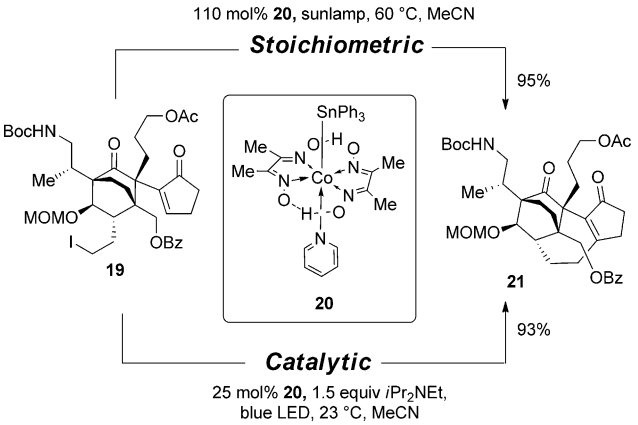
The mixture of epimers at C(18) in **16** could not be separated by chromatography on silica gel at this stage. Reduction of **16** with Zn/NH_4Cl(aq) in EtOH[17] afforded an



Scheme 5. Reagents and conditions: a) $CeCl_3 \cdot x H_2O$, oxalic acid, MeCN, RT, 98%; b) Me_3S/imidazole, CH_2Cl_2, RT; MOMCl, iPr_2NEt, CH_2Cl_2, RT, TBAF, THF, RT, 90%; c) DMP, CH_2Cl_2, RT, 99%; d) $MeNO_2$, NH_4OAc, 75 °C, 77%. e) $ZnMe_2$, $[Cu(OTf)]_2 \cdot$toluene, **L1**, toluene, 0 °C, d.r. = 5:1, 90% comb. yield; f) Zn, aq NH_4Cl, EtOH, 40 °C; Boc_2O, EtOH, RT, 85%; g) O_3, PPh_3, CH_2Cl_2, −78 °C; $NaBH(OAc)_3$, AcOH, THF, RT, 72%; h) MsCl, Et_3N, CH_2Cl_2, 0 °C. NaI, acetone, 76%; i) DBU, toluene, RT, 92%. Boc_2O = di-*tert*-butyl dicarbonate, Ms = methylsulfonyl, DBU = diazabicycloundecane; MOM = methoxymethyl.

intermediate primary amine cleanly, which, to our surprise and in contrast to previously investigated systems, did not spontaneously condense to form the imine.[21] Treatment of the crude reaction mixture with Boc anhydride yielded **17** (85%), and at this point the minor C(18) epimer arising from the conjugate addition could be separated by chromatography on silica gel.[20] Ozonolysis of **17**, followed by reductive workup (PPh_3) and selective reduction ($NaBH(OAc)_3$) of the aldehyde afforded primary alcohol **18** (72% over 2 steps). Conversion of the hydroxy group to an iodide under standard conditions (MsCl, then NaI, 76%) and DBU promoted elimination of the MOM-protected alcohol (92%) to afford enone **19**.

Extensive experimentation was required to find conditions for the formation of the octahydroazulene domain. A collection of transformations were examined with which to effect the cyclization. These included free-radical conditions, SmI2-induced Barbier reactions, as well as Pd-, Cr-, and Co-mediated cyclizations.[22–24] Thus, it was found that treatment of iodide **19** with 1.1 equivalents of cobaloxime **20**[24] under irradiation with a sunlamp afforded cyclized enone **21** in 95% yield (Scheme 6).[25] Inspired by this successful application of a cobaloxime-mediated Heck cyclization, we subsequently developed a protocol that requires only catalytic amounts of **20** in combination with a stoichiometric amount of Hünig's base. This novel method provides an efficient complement to palladium-catalyzed alkyl-Heck coupling reactions and significantly expands the applicability of this transformation.

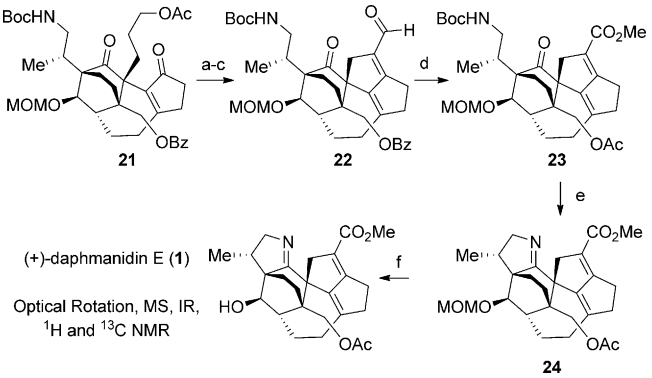


Scheme 6. Alkyl-Heck cyclization of **19**.

The full scope of this method, which is catalytic in cobaloxime **20**, has been studied in parallel and will be reported separately. It is worth noting that the cyclization secures the assignment of the configuration at C(8), which had arisen from a Claisen rearrangement earlier in the synthesis.

Selective saponification of the acetate group in **21** (K_2CO_3/MeOH at 0 °C, 77%) liberated an alcohol, which was oxidized with PCC to the corresponding aldehyde (92%; Scheme 7). An intramolecular aldol condensation was realized by heating the aldehyde in the presence of $Bn_2NH_2 \cdot O_2CCF_3$. Prolonged exposure of product **22** to these conditions led to decomposition. Consequently, it was optimal to carry out the reaction to approximately 70% conversion and recover the starting material. After two cycles, the overall yield of **22** was 77%.

α,β,γ,δ-Unsaturated aldehyde **22** was then cleanly oxidized to the corresponding methyl ester by using Corey's procedure[26] and the benzoic ester was exchanged for an acetate group, thereby affording **23** (79% over 3 steps). Removal of the *N*-Boc group was achieved under standard conditions (10% CF_3CO_2H in CH_2Cl_2) and the resulting



Scheme 7. Reagents and conditions: a) K_2CO_3, MeOH, 0 °C, 77%; b) PCC, CH_2Cl_2, RT, 92%; c) $Bn_2NH \cdot CF_3CO_2H$ (1:1), PhH, 50 °C, 77% after 1 recycle; d) NaCN, AcOH, MnO_2, MeOH, RT; K_2CO_3, MeOH, 45 °C; Ac_2O, iPr_2NEt, DMAP, CH_2Cl_2, RT, 79% over 3 steps. e) CF_3CO_2H, CH_2Cl_2, RT; NH_4Cl, EtOH, 75 °C, 56%; f) Ph_2BBr, CH_2Cl_2, −25 °C, 76%. PCC = pyridinium chlorochromate.

ammonium salt was stirred for 24 h at 75 °C in EtOH to bring about condensation to afford the imine.

The observed obduracy of the amine to condense with the ketone was quite surprising. A plausible explanation for the slow condensation could be the unfavorable steric interactions with the adjacent quaternary centers that arise in a tetrahedral intermediate. Finally, removal of the MOM group was achieved cleanly with Ph_2BBr[27] at −25 °C and afforded (+)-daphmanidin E (**1**), which was fully characterized by 2D NMR spectroscopy. Titration of an NMR sample with TFA (1.3 equiv) afforded ^1H and ^{13}C NMR spectra which were in good agreement with the reported data.[28] Moreover, comparison of the sign of the optical rotation with the reported value confirmed the assigned absolute stereochemistry (synthetic: $[\alpha]_D^{22} = +43.1°$, $c = 0.1$; reported: $[\alpha]_D^{20} = +11°$, $c = 0.5$).[29]

In summary, we have documented the first total synthesis of a member of the daphmanidin alkaloids, namely (+)-daphmanidin E. The synthesis is based on a versatile, C_2-symmetric building block and relies on a series of highly diastereoselective transformations to set the relative stereochemistry at the bicyclo[2.2.2]octanone core. Additional salient features of the synthesis include two Claisen rearrangements to install a hindered quaternary stereogenic center at C(8) and the use of a copper/peptide complex as a catalyst for a reagent-controlled stereoselective conjugate addition. Moreover, a key feature of the strategy is the late-stage ring closure of an alkyl iodide onto an enone to form the seven-membered carbocycle. This is made possible through the implementation of a cobalt-catalyzed Heck coupling reaction. The strategy and tactics we delineate are relevant to studies involving the large number of daphniphyllum alkaloids that have recently been isolated.

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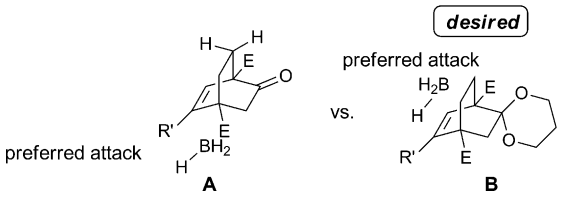

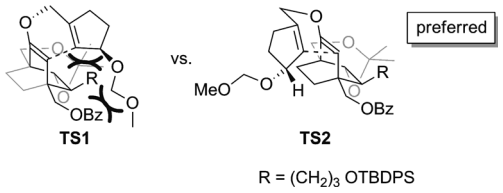

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[28] Significant differences in the ^{1}H NMR spectrum were observed if a sample of the iminium salt was dried under high vacuum before the measurement. Titration with incremental amounts of TFA showed that the chemical shifts in the ^{1}H NMR spectrum of **1** change significantly with an increasing degree of imine protonation.

[29] A significant deviation in the magnitude of the optical rotation of synthetic **1** and the reported value was noted. This discrepancy could not be explained, but was tentatively attributed to the unknown purity and degree of protonation of a sample of **1** isolated from natural sources.

