Natural Products Synthesis

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Substrate-Controlled Asymmetric Total Synthesis of (+)-Microcladallene B with a Bromination Strategy Based on a Nucleophile-Assisting Leaving Group**

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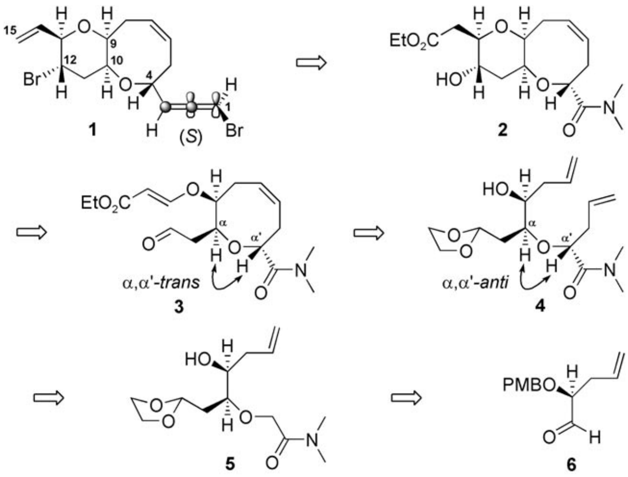
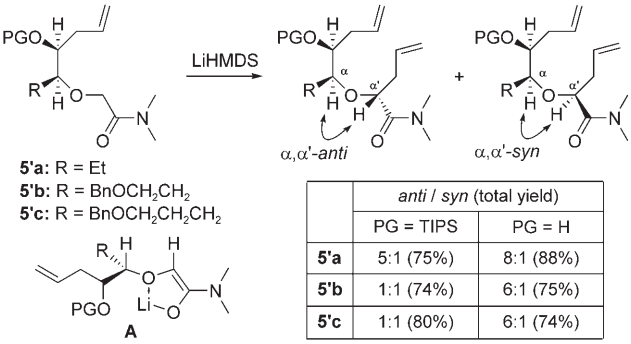
(+)-Microcladallene B (**1**) was isolated by Kennedy et al. from the red alga *Laurencia microcladia* collected off the French coast at Cap Ferrat.[1] The structure and absolute configuration of the C_{15} acetogenin were assigned by a combination of spectroscopic analysis and X-ray crystallography.[1] The key structural features of the marine natural product are 1) a unique *cis*-fused 2,9-dioxabicyclo-[6.4.0]dodecane skeleton composed of an α,α′-*trans* oxocene and a tetrahydropyran ring, 2) an *S* bromoallene appendage, and 3) a secondary bromide functionality.[2] The successful execution of a synthesis of the halogenated medium-sized oxacyclic natural product hinges upon the stereoselective incorporation of the bromine functionality at C12, which is recognized to be a significant challenge.[3] Herein, we report the first and completely substrate-controlled asymmetric total synthesis of (+)-microcladallene B (**1**). Our synthesis features a novel dianion alkylation to provide the α,α′-*anti* substrate for ring-closing metathesis (RCM), a chemoselective RCM to form the oxocene, a SmI_2-mediated reductive cyclization to construct the *cis*-fused dioxabicyclic core, and a novel application of methodology based on a nucleophile-assisting leaving group (NALG) for the stereoselective introduction of the bromine functionality at C12.

We envisaged that (+)-microcladallene B (**1**) could be elaborated from the dioxabicyclic compound **2** by an NALG bromination method (Scheme 1).[4] The *cis*-fused dioxabicylic intermediate **2** could be prepared in turn by a SmI_2-mediated reductive cyclization[5] of the β-alkoxy acrylate **3**. We further envisaged that the key α,α′-*anti* RCM substrate **4** could be secured stereoselectively by alkylation of the dianion derived from the hydroxyamide **5** without resorting to the use of a chiral auxiliary. Further analysis suggested that the hydroxyamide **5** should be readily accessible from the known aldehyde **6** through a Grignard reaction.



Scheme 1. Retrosynthetic analysis of (+)-microcladallene B (**1**). PMB = *p*-methoxybenzyl.

Our study commenced with the exploration of a direct stereoselective route to the α,α′-*anti* RCM substrate **4**. Recently, we reported that the "protecting-group-dependent" alkylation of the TIPS-protected α-alkoxy amide **5′a** (PG = TIPS) with allyl bromide furnished the corresponding α,α′-*anti* bisalkene with 5:1 stereoselectivity by electrophilic attack from the side of the smaller (ethyl) group in the H,H-eclipsed conformation shown by the monodentate model **A** (Scheme 2).[6] In an ensuing study, we observed that *anti*/*syn* stereoselectivity diminishes as the R group becomes larger, as illustrated by the results obtained with the TIPS-protected amides **5′b** and **5′c** (PG = TIPS). However, we were delighted to find that the corresponding unprotected hydroxyamides **5′a–c** (PG = H) reacted to furnish the desired α,α′-*anti* bisalkenes with high stereoselectivity under similar conditions (Scheme 2), presumably via a dianion.



	anti / syn (total yield)	
	PG = TIPS	PG = H
5'a	5:1 (75%)	8:1 (88%)
5'b	1:1 (74%)	6:1 (75%)
5'c	1:1 (80%)	6:1 (74%)

Scheme 2. Dianion alkylation of hydroxyamides. Bn = benzyl, HMDS = hexamethyldisilazide, TIPS = triisopropylsilyl.

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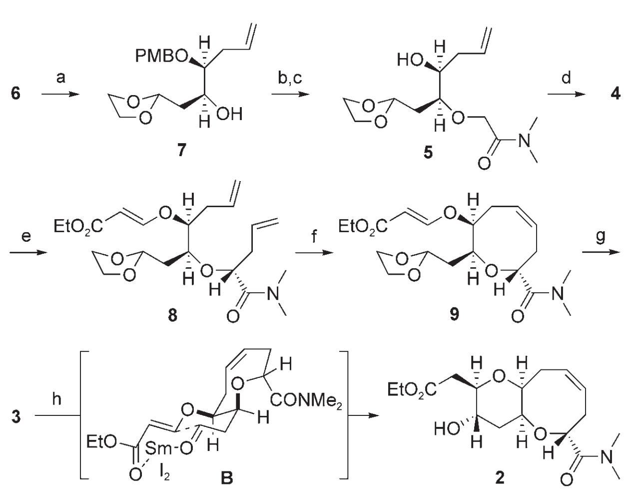
Having developed a suitable dianion-alkylation protocol, we began the synthesis of **1** by the addition of commercially available (1,3-dioxolan-2-ylmethyl)magnesium bromide to the known aldehyde **6**[7] to furnish the desired *syn* alcohol **7** in 67% yield with 10:1 *syn*/*anti* stereoselectivity (Scheme 3).

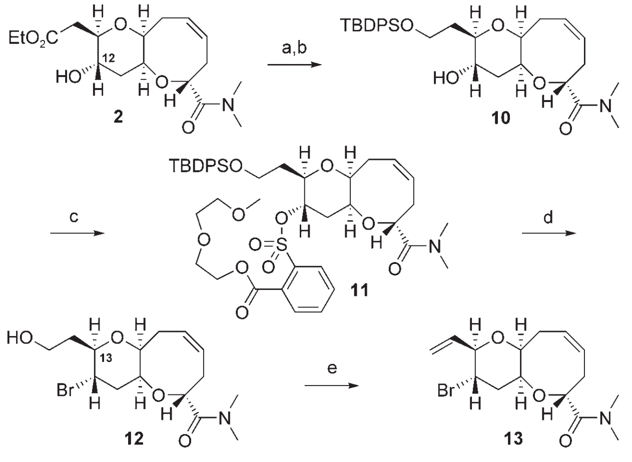


Scheme 3. Construction of the bicyclic core fragment **2**: a) (1,3-dioxolan-2-ylmethyl)magnesium bromide, THF, 60°C, 1.5 h, 67%; b) NaH, THF, 0°C, 30 min, then $ClCH_2CONMe_2$, RT, 30 min, 99%; c) DDQ, CH_2Cl_2/pH 7.4 buffer (9:1), 0°C→RT, 1 h, 99%; d) LiHMDS, allyl iodide, THF, −78°C to −45°C, 3 h, 63%; e) ethyl propiolate, NMM, CH_2Cl_2, room temperature, 16 h, 99%; f) $[Cl_2\{(c\text{-}C_6H_{11})_3P\}_2Ru{=}CHPh]$, CH_2Cl_2, room temperature, 18 h, then DMSO, room temperature, 10 h, 91%; g) PPTS, acetone, H_2O, 130°C, 5 h, 73%; h) SmI_2, MeOH, THF, room temperature, 1.5 h, 85%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMSO = dimethylsulfoxide, NMM = *N*-methylmorpholine, PPTS = pyridinium *p*-toluenesulfonate.

O Alkylation of the *syn* alcohol **7** with *N*,*N*-dimethyl-α-chloroacetamide, followed by oxidative removal of the PMB group of the resulting α-alkoxy amide with wet DDQ,[8] then provided the corresponding hydroxyamide **5** in excellent yield (98%, two steps) to set the stage for the crucial dianion alkylation. To our satisfaction, the treatment of hydroxyamide **5** with LiHMDS followed by allyl iodide produced the desired α,α′-*anti* isomer **4** in 63% yield with 6:1 *anti*/*syn* stereoselectivity.

With the key α,α′-*anti* isomer **4** in hand, we proceeded to address the construction of the dioxabicyclic core by using an RCM reaction[9] and the protocol described by Nakata and co-workers for SmI_2-mediated reductive cyclization.[5] We were pleased to find that triene **8**, prepared from the diene alcohol **4** by treatment with ethyl propiolate,[10] underwent an efficient chemoselective RCM reaction to deliver the key oxocene **9** in excellent overall yield (90%, two steps). Hydrolysis of the acetal functionality in **9** under carefully controlled acidic conditions, followed by SmI_2-mediated pyranoannulation of the resultant aldehydo β-alkoxy acrylate **3**, gave the key dioxabicycle **2** in 62% yield for the two steps in a 13:1 α/β-OH ratio at C12. The preferred geometry of the transition state for this cyclization is probably described by **B**.[11]

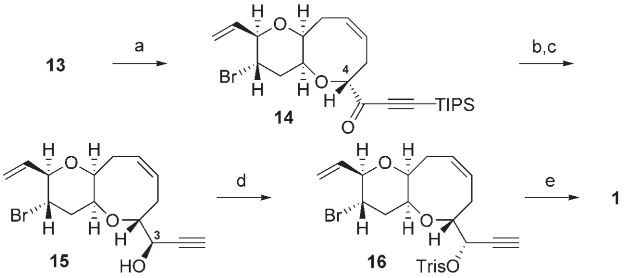
Following the construction of the dioxabicyclic core of (+)-microcladallene B (**1**), we set out to tackle the formidable[3] task of introducing the C12 bromine functionality with retention of configuration (Scheme 4). The chemoselective reduction of ester **2** with $LiBH_4$[12] and selective protection of the primary hydroxy group in the resulting diol with TBDPSCl led to the secondary alcohol **10** (83%, two steps) and set the stage for the pivotal bromination. As anticipated, the stereoselective introduction of the bromine functionality at C12 proved to be extremely problematic. Our extensive efforts to brominate the α alcohol **10**, which has an equatorial hydroxy group, and the corresponding β alcohol, in which the hydroxy group has an axial orientation, under a variety of conditions led to unsatisfactory results.[13]



Scheme 4. NALG bromination: a) $LiBH_4$, MeOH, Et_2O, 0°C→RT, 2 h, 84%; b) TBDPSCl, imidazole, CH_2Cl_2, RT, 1 h, 99%; c) 2-$[CH_3(OC_2H_4)_2OC(O)]C_6H_4SO_2Cl$, DMAP, CH_2Cl_2, room temperature, 4 h, 92%; d) $TiBr_4$, CH_2Cl_2, 0°C→RT, 2 h, 63%; e) 2-$NO_2C_6H_4SeCN$, $(n\text{-}C_8H_{15})_3P$, THF, 0°C→RT, 2 h, then H_2O_2, 0°C→RT, 10 h, 91%. DMAP = 4-dimethylaminopyridine, TBDPS = *tert*-butyldiphenylsilyl.

After considerable experimentation, we were delighted to find that the treatment of aryl sulfonate **11**, which has an NALG with a chelating polyether unit, with titanium tetrabromide by using a modification of the chlorination protocol of Lepore and co-workers[4] furnished the desired α bromide, probably through an S_Ni mechanism, with concomitant cleavage of the TBDPS ether to give **12** in 63% yield. The hydroxyethyl group at C13 of bromoalcohol **12** was then transformed into the requisite vinyl group in a one-pot process by the protocol described by Grieco et al. to furnish alkene **13** in good yield (91%).[14]

Having properly functionalized the tetrahydropyranyl moiety, we next directed our attention to the stereoselective assembly of the bromoallene appendage at C4 to complete the synthesis (Scheme 5). The use of our protocol for direct ketone synthesis[15] with the α-alkoxy amide **13** and TIPS-substituted acetylene under Yamaguchi conditions[16] afforded the ynone **14** in 84% yield. The highly stereoselective and efficient reduction of ketone **14** with L-selectride[17] in a Felkin–Ahn sense, followed by removal of the TIPS group in the resulting alcohol by exposure to TBAF, led exclusively to the 3*R* propargylic alcohol **15** (77%, two steps). Alcohol **15** was then converted into the required 3*S* trisylate **16** in a single



Scheme 5. Completion of the synthesis of (+)-microcladallene B (**1**): a) $BF_3\cdot Et_2O$, TIPS−C≡CH, *n*BuLi, THF, −78 °C, 2 h, 84 %; b) L-selectride, THF, −78 °C, 1 h, 91 %; c) TBAF, THF, 0 °C→RT, 1 h, 85 %; d) 2,4,6-$iPr_3C_6H_2SO_3H$, DIAD, Ph_3P, Et_3N, THF, 60 °C, 2 h, 56 %; e) LiBr, CuBr, THF, 60 °C, 8 h, 73 %. DIAD = diisopropylazodicarboxylate, TBAF = tetrabutylammonium fluoride, Tris = 2,4,6-triisopropylbenzenesulfonyl.

step by using the modification by Anderson et al. of the procedure described by Galynker and Still.[18] Finally, S_N2' displacement of the trisylate group upon the exposure of **16** to $LiCuBr_2$ delivered (+)-microcladallene B (**1**) in 73 % yield along with a small amount of the corresponding product of S_N2 substitution.[19] The optical-rotation data for synthetic (+)-microcladallene B were in close agreement with those of the natural product: $[\alpha]_D^{20} = +93.2$ ($c = 0.14$, Me_2CO; lit.[1]: $[\alpha]_D^{20} = +96.0$ ($c = 0.50$, Me_2CO)).[20,21]

In conclusion, we have completed an asymmetric total synthesis of (+)-microcladallene B (**1**) in 18 steps and 3 % overall yield from the readily available aldehyde **6** in a substrate-controlled fashion. Highlights of the synthesis include a novel dianion alkylation for the synthesis of the α,α′-*anti* substrate for RCM and a novel application of NALG methodology for the demanding stereoselective introduction of the bromine substituent at C12. The application of the NALG halogenation to the synthesis of other natural products is under investigation in our laboratories.

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Keywords: bromination · dianion alkylation · natural products · nucleophile-assisting leaving groups · total synthesis

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[21] Characterization of synthetic **1**: $R_f = 0.21$ (hexane/ethyl acetate, 10:1); m.p. 84–88 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.11$ (1 H, dd, $J = 5.9$, 2.8 Hz, 1 H), 5.85–6.00 (m, 2 H), 5.81 (ddd, $J = 17.2$, 10.3, 10.3 Hz, 1 H), 5.41–5.45 (m, 2 H), 5.32 (d, $J = 10.5$ Hz, 1 H), 4.83 (ddd, $J = 7.2$, 3.5, 3.5 Hz, 1 H), 4.08 (ddd, $J = 12.4$, 10.1, 4.3 Hz, 1 H), 3.89 (dd, $J = 10.2$, 6.8 Hz, 1 H), 3.83 (bs, 1 H), 3.69 (dd, $J = 9.8$, 4.6 Hz, 1 H), 2.65–2.67 (m, 1 H), 2.60 (ddd, $J = 12.8$, 9.8, 3.0 Hz, 1 H), 2.52 (ddd, $J = 7.8$, 3.8, 3.8 Hz, 1 H), 2.27–2.33 (m, 2 H), 2.17 ppm (ddd, $J = 12.7$, 11.5, 3.2 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 202.6$, 135.4, 129.3, 128.7, 119.4, 100.0, 83.3, 80.6, 74.9, 74.4, 69.9, 48.0, 43.2, 31.7, 30.2 ppm.