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Authors: Thomas Lindel, Jan Hendrik Lang, and Peter G. Jones

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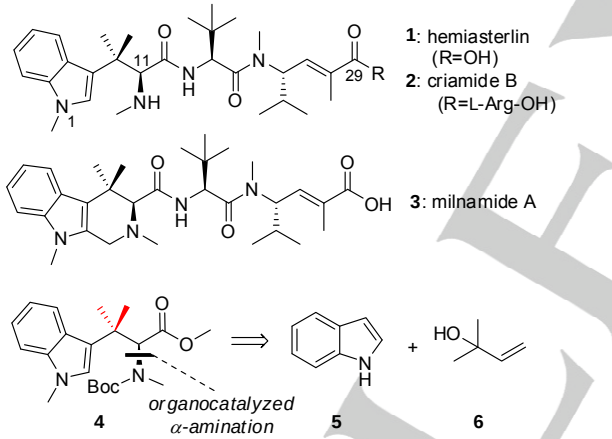
Total synthesis of the marine natural product hemiasterlin via organocatalyzed α-hydrazination

Jan Hendrik Lang[a], Peter G. Jones[b], and Thomas Lindel[a]*

Dedicated to Professor Stefan Schulz on the occasion of his 60th birthday

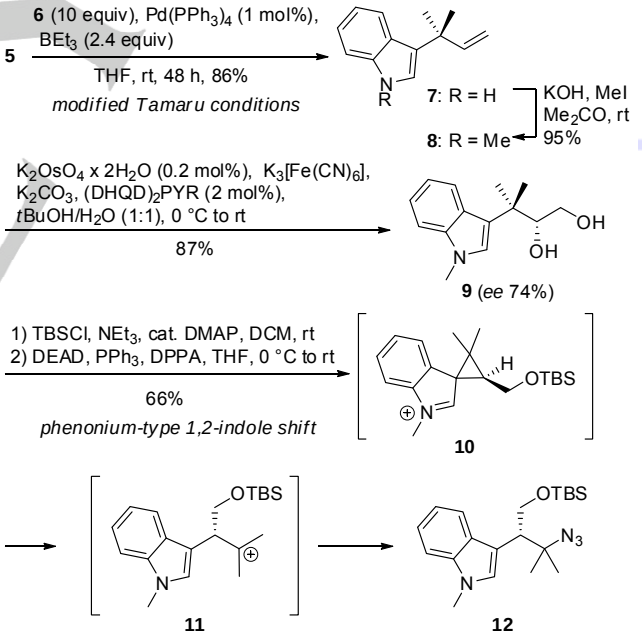
Abstract. An efficient synthesis of the potently cytotoxic marine peptide hemiasterlin is presented. The tetramethyltryptophan moiety is assembled via *tert.*-prenylation of indole, followed by the high-yielding, organocatalyzed α-hydrazination of a sterically congested aldehyde with excellent enantioselectivity. BEP-mediated peptide coupling completes the synthesis, being the first approach that does not employ chiral auxiliaries. A novel phenonium-type rearrangement of the indole system occurred when subjecting dihydroxylated 3-*tert.*-prenylindole to Mitsunobu conditions.

Hemiasterlin (**1**, Scheme 1) and its structural analogs criamide B (**2**) and milnamide A (**3**) constitute highly cytotoxic marine natural products isolated from sponges.[1] The excellent antimitotic activity of hemiasterlin (**1**)[2] is based on microtubule depolymerization and has triggered clinical trials of **1** as an anticancer agent.[3] The methylation pattern of the tryptophan-derived section is crucial for the bioactivity of hemiasterlin (**1**).[4b]



Scheme 1. Hemiasterlin (**1**) and structurally related criamide B (**2**) and milnamide A (**3**); access to tetramethyltryptophan **4**.

To date, two total syntheses of hemiasterlin (**1**) and one synthesis of the challenging tetramethyltryptophan derivative **4** have been published. Andersen et al. started from indol-3-ylacetic acid employing Evans' oxazolidinone chemistry.[4] Vedejs and Kongkittingam installed the amino nitrogen atom by an asymmetric Strecker reaction, employing (*R*)-2-phenylglycinol as chiral auxiliary.[5] Durst et al. published a shortened Strecker route to **4**.[6] Molinski et al. achieved the total synthesis of the closely related milnamide A (**3**) by oxidative rearrangement of a phenylglycinol-based oxazoline intermediate.[7] We felt that an enantioselective route to the tetramethylated tryptophan derivative **4** should be developed without using chiral auxiliaries. For the assembly of the complete carbon framework in one step, Tamaru's 3-*tert.*-prenylation of indole (**5**) was employed (Scheme 2).[8] By reducing the catalyst load from 5 mol% to 1 mol% and by using 10 equiv. of *tert.*-prenol (**6**) at r.t., we obtained the desired regioisomer **7** exclusively (86%), which was *N*-methylated affording **8** (95%).



Scheme 2. Regioselective *tert.*-prenylation of indole (**5**) and 1,2-aryl shift of diol **9** instead of an S_N2 azide replacement.

We first intended to install the stereogenic center of **4** via Sharpless asymmetric dihydroxylation (AD). *Tert.*-prenyl partial structures have rarely been dihydroxylated under Sharpless conditions[9] and there appears to be no example starting from *tert.*-prenylarenes. We employed the $(DHQD)_2PYR$ ligand, which was reported to provide improved enantioselectivity for monosubstituted alkenes (Scheme 2).[10] Diol **9** was obtained from **8** in convincing yield (87%, *ee* 74%) and converted to the mono-TBS-ether, which was subjected to Mitsunobu conditions

[a] M. Sc. J. H. Lang, Prof. Dr. T. Lindel
Institute of Organic Chemistry
Technical University Braunschweig
Hagenring 30, 38106 Braunschweig, Germany
E-mail: th.lindel@tu-braunschweig.de
Homepage: www.oc.tu-bs.de/lindel
[b] Prof. Dr. Peter G. Jones
Institute of Inorganic and Analytical Chemistry
Technical University Braunschweig
Hagenring 30, 38106 Braunschweig, Germany

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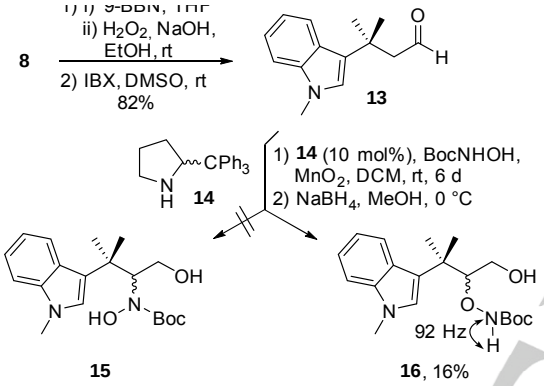
with diphenylphosphorylazide (DPPA) as azide source. We obtained a product with the expected molecular formula, implying the desired replacement of the hydroxy by an azido group. However, the carbon skeleton of starting material **9** had undergone rearrangement affording tertiary azide **12** via an indole 1,2-shift.[11] Presumably, *spiro* cyclopropane **10** with an iminium function is formed, followed by ring opening to tertiary carbocation **11**, which is attacked by azide forming product **12**.[12] The behavior of compound **9** differs from Durst's results, where intermolecular S_N reaction in the neopentyl position was indeed possible starting from a β,β-dimethylated α-hydroxyester.[6]

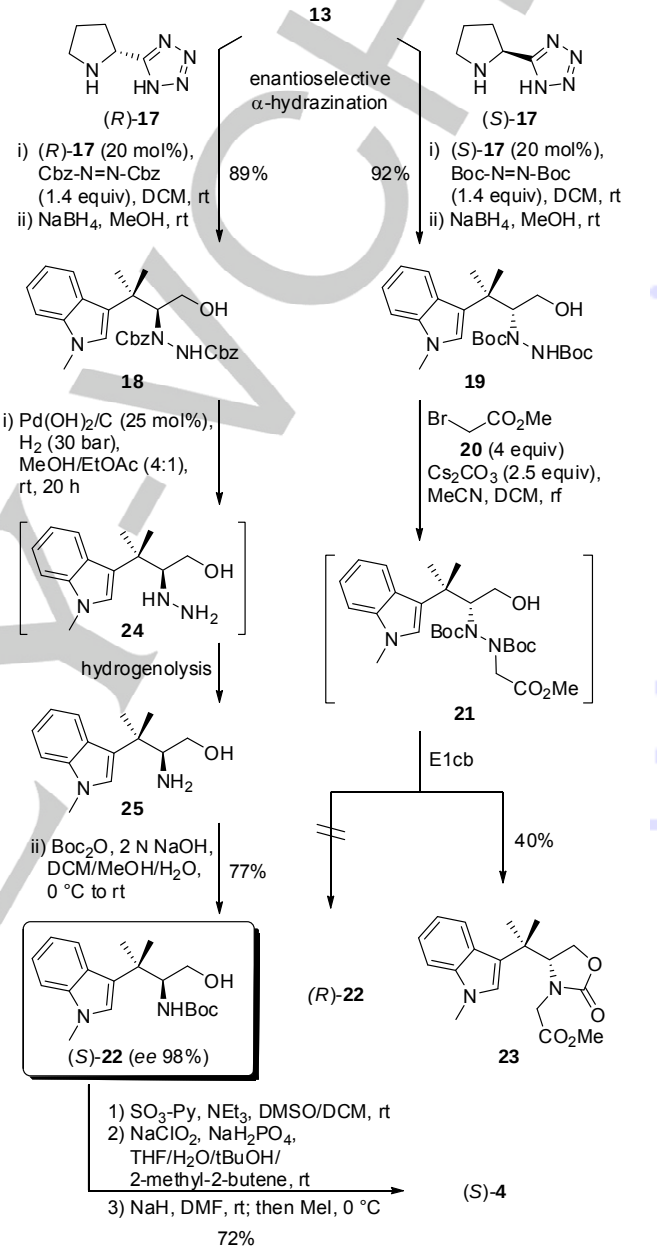
We abandoned the Sharpless AD approach and converted *tert.*-prenylindole **8** to aldehyde **13** by hydroboration (9-BBN) and oxidation (IBX, Scheme 3), because an enantioselective, organocatalyzed α-amination of **13** appeared to be a viable alternative.[13]



Scheme 3. Attempted α-hydroxyamination of aldehyde **13** with racemic catalyst **14**, adapting Maruoka's protocol.[14]

Maruoka et al.[14] had reported the enamine-catalyzed α-hydroxyamination of aliphatic aldehydes. One example was neohexyl aldehyde, which, in the presence of (2*R*)-2-tritylpyrrolidine (**14**) as catalyst, had reacted with *tert.*-butyl nitrosoformate to form *N*-Boc-protected α-hydroxyamino products with an *ee* of 99%.[15] Adapting Maruoka's protocol, we used 10 mol% of the catalyst *rac*-**14**.[16] The product was obtained only in low yield (16%) and displayed a ^{13}C NMR resonance ($CDCl_3$) at 97.5 ppm for the aliphatic CH, very similar to the chemical shift of 98.9 ppm reported by Maruoka et al. for the hydroxyamination product of neohexyl aldehyde.[14] This suggested that aminooxylation instead of hydroxyamination had taken place. In the $^{1}H,^{15}N$ HMBC spectrum of **16**, we observed an estimated $^{1}J_{HN}$ coupling constant of 92 Hz, indicating that the newly introduced nitrogen was protonated.

Symmetrically substituted azodicarboxylates such as DEAD would eliminate the problem of N,O selectivity and afford hydrazine dicarboxylates. With di-*tert.*-butyl and dibenzyl azodicarboxylate, organocatalyzed α-hydrazination of **13** proceeded smoothly and delivered the protected hydrazine dicarboxylates **18** and **19**. We employed chiral (2*S*)- and (2*R*)-5-(2-pyrrolidinyl)-1*H*-tetrazole (**17**) catalysts.[17] The resulting aldehydes were reduced ($NaBH_4$, MeOH) to the stable alcohols providing **18** and **19** in excellent yields (92% for the Boc and 89% for the Cbz derivative over two steps). The successful α-hydrazination is one of the few examples starting from neohexyl aldehydes.[18] The reaction was, in the case of the Cbz-derivative **18**, run on a 5 mmol scale.



Scheme 4. Enantioselective synthesis of trimethylated tryptophanol derivative **22** via organocatalyzed α-hydrazination of the β,β-dimethylated aldehyde **13**, followed by conversion to tetramethyl-tryptophan **4**.

X-ray analysis of the Boc-protected hydrazine derivative (*R*)-**19** revealed an intramolecular hydrogen bond between O1-H and O4 forming an eight-membered ring (Figure 1). This conformation may also be present in solution ($CDCl_3$), since we observed a sharp doublet of doublets for the hydroxy proton of the main rotamer, with coupling constants $^{3}J_{HH}$ = 11.7 Hz, 3.1 Hz that

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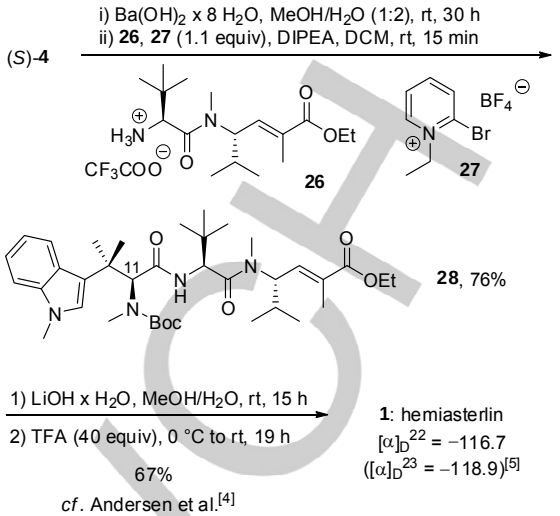
indicate antiperiplanar and *gauche*-positioned methylene hydrogen atoms.

(*R*)-**19**

Figure 1. X-ray structure of Boc-protected hydrazine derivative (*R*)-**19** obtained by α-hydrazination of aldehyde **13** employing (*S*)-**17** as organocatalyst, followed by reduction (CCDC 1554937).

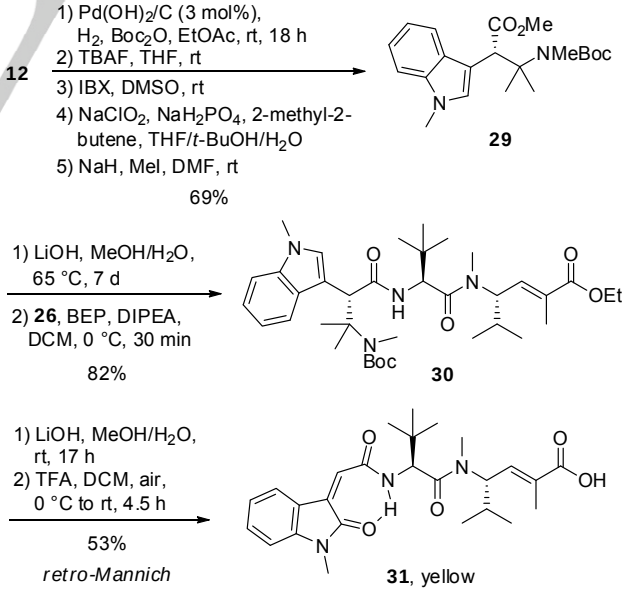
To our dismay, N-N cleavage was more capricious than expected. Using SmI_2 requires the secondary nitrogen to be trifluoroacetylated, which facilitates reductive cleavage of the N-N bond.[18b,c] Magnus et al. had alkylated a secondary amine with bromoacetate **20**, which undergoes E1cb elimination upon treatment with Cs_2CO_3.[19] Both methods failed in our case, with oxazolidinone **23** being the only isolated product when following the Magnus protocol (Scheme 4). Hence, we investigated hydrogenolytic methods. While treatment of doubly Cbz-protected hydrazine **18** with 1 bar H_2/Raney-Ni, Pd/C or PtO_2 failed, we observed N-N cleavage when using polymethylhydrosiloxane (PMHS) as "green chemistry" H_2 equivalent and $PdCl_2$ as catalyst.[20] However, the reaction was not reliable. Use of Pearlman's catalyst ($Pd(OH)_2$/C, 25 mol%) in EtOAc/MeOH (1:4) at 30 bar at r.t. (Parr pressure vessel) proved to be optimal (up to 1 mmol scale). After treatment of the free amino alcohol **25** with Boc_2O, the desired *N*-Boc-protected amino alcohol **22** was obtained in good yield (77% over two steps). The *ee* values of (*S*)-**22** (98%) and of (*R*)-**22** (97%, obtained when using catalyst (*S*)-**17**, not shown) were determined on a chiral HPLC column (CHIRALPAK IA, *n*-hexane/*i*PrOH 99:1), proving the excellent enantioselectivity of the organocatalyzed hydrazination reaction. Parikh-Doering oxidation of amino alcohol **22** provided the amino aldehyde, which was oxidized under Lindgren-Pinnick conditions in THF/*t*-BuOH/water.[21] Alternatives such as K_2CO_3/ *N*-iodosuccinimide[22] led to decomposition. Methylation (NaH, MeI, DMF) delivered the Andersen intermediate **4**.[4]

With a view to peptide coupling with dipeptide **26**,[4b] methyl ester **4** was saponified using a suspension of $Ba(OH)_2 \cdot 8H_2O$ in MeOH/water in a temperature-controlled ultrasonic bath. Efficient coupling was discovered when using BEP (2-bromo-*N*-ethylpyridinium tetrafluoroborate, **27**), a derivative of Mukaiyama's coupling reagent,[23] and Hünig's base, which proved to be superior to PyBroP.[4] Boc-protected hemiasterlin ethyl ester **28** was obtained in 76% yield after only 15 min (Scheme 5).



Scheme 5. Synthesis of hemiasterlin (**1**) via BEP-mediated amide coupling.

Ethyl ester **28** was saponified with LiOH-H_2O[4] and after work-up, the crude *N*-Boc-protected hemiasterlin was treated with TFA (40 equiv.) in DCM. Hemiasterlin (**1**) was isolated in 67% yield (2 steps). The salt-free form of **1**, obtained after normal phase chromatography, exhibited zwitterion characteristics as proposed by Kashman.[1a] The optical rotatory power of our product **1** in MeOH ($[\alpha]_D^{22}$ = −116.7 at *c* = 0.06 g/100 mL) compares well with the value obtained by Vedejs ($[\alpha]_D^{23}$ = −118.9 at *c* = 0.07 g/100 mL).[5] From (*R*)-**22** we also synthesized 11-*epi*-hemiasterlin (see the SI), which showed a lower optical rotatory power ($[\alpha]_D^{22}$ = −62.3 at *c* = 0.26 g/100 mL).



Scheme 6. Formation of the yellow alkylidene indolone **31** starting from β-tetramethyltryptophan **29**.

Finally, we became curious as to whether our rearranged Mitsunobu product **12** could also be transformed to the corresponding amino acid (Scheme 6). A five-step sequence

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afforded β-amino acid **29**, which was saponified and coupled (BEP) with peptide **26** (82%, two steps). Saponification of **30** went smoothly. However, we were not able to obtain the free secondary amine. Instead, treatment of the carboxylic acid with excess TFA in the presence of air afforded a yellow product in good yield (53%). An unprecedented retro Mannich reaction had occurred, followed by oxidation of the resulting indole acetic acid moiety to the 3-alkylidene indolone **31**. In the ^{1}H NMR spectrum, the amide proton appeared as a sharp doublet at 11.18 ppm, indicating an intramolecular hydrogen bond to the indolone oxygen.

In conclusion, we have developed a novel enantioselective route to the sterically congested tetramethyltryptophan moiety of hemiasterlin (**1**). Our approach encompasses 11 steps (31% overall yield) starting from indole, avoids the use of chiral auxiliaries, and features a high-yielding organocatalyzed α-hydrazination. By employing BEP peptide coupling, hemiasterlin (**1**) was obtained in a very efficient manner. A novel phenonium-type rearrangement of the *tert.*-prenylated indole system under Mitsunobu conditions was discovered.

Acknowledgements
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Keywords: total synthesis, natural products, organocatalysis, peptides, rearrangement.

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Entry for the Table of Contents

Total synthesis

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