Progress towards the Total Synthesis of Scytonemin A: Asymmetric Synthesis of (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline

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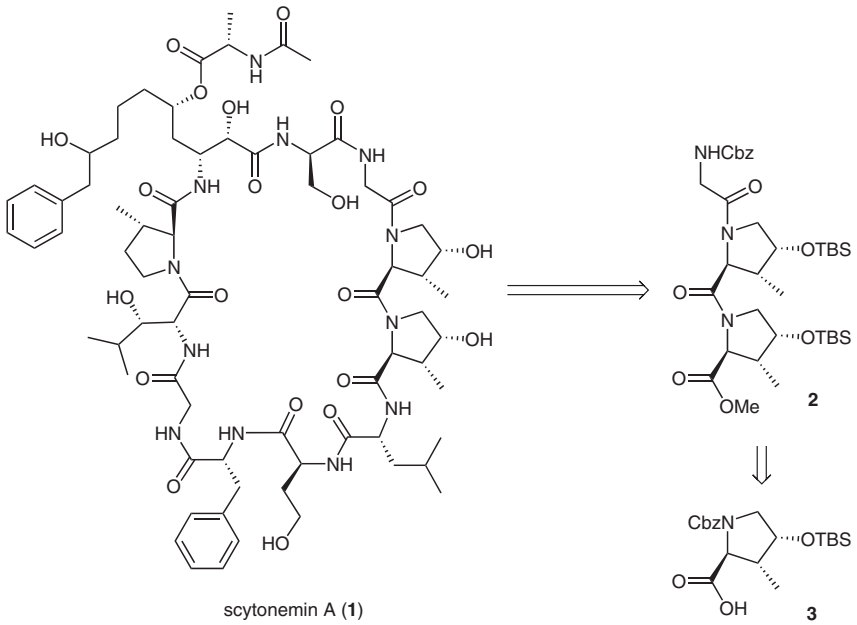
Dedicated to Gerry Pattenden on the occasion of his 70th birthday

Abstract: During the total synthesis of the novel cyclopeptide scytonemin A, the fragment containing two (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline units was successfully prepared. Two approaches leading to (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline have been explored. They involve the following key transformations: asymmetric crotylation, Sharpless epoxidation–subsequent epoxide opening, intramolecular amidomercuration–oxidation.

Key words: scytonemin A, cyclopeptide, substituted proline, amino acids, asymmetric synthesis

Marine organisms have provided chemists with a wealth of structurally diverse compounds in recent years, and many of these compounds have shown considerable biological activity including antimicrobial, antiviral, antitumor, and anti-inflammatory properties.[1] Some of these compounds are in advanced clinical trials, and others have proven useful in studies directed toward the elucidation of biochemical pathways.[1,2] In 1988, Moore et al. reported the isolation of an unusual cyclic peptide, scytonemin A (Scheme 1), from a *Scytonema* sp. (strain U-3-3, *Scytonemataceae*).[3] The structure of scytonemin A was determined by interpretation of spectroscopic data, chemical degradation, and evaluation of the amino acids obtained by acid hydrolysis.

In our efforts to synthesize a series of bioactive cyclopeptides and cyclodepsipeptides,[4] we chose scytonemin A (**1**) as a target due to its potent calcium antagonistic properties and its novel amino acid residues: (2*R*,3*S*)-*threo*-3-hydroxyleucine (HyLeu), (2*S*,3*S*)-*trans*-3-methylproline (MePro), (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline (Hy



Scheme 1 Structure of scytonemin A

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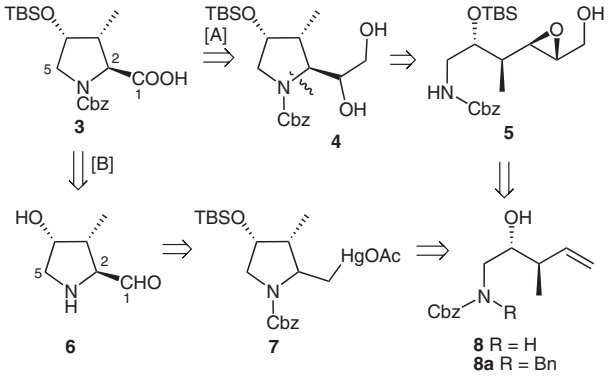
MePro), and (2*S*,3*R*,5*S*)-3-amino-2,5,9-trihydroxy-l0-phenyldecanoic acid (Ahda). En route to a total synthesis of scytonemin A (**1**), we have developed two novel stereocontrolled asymmetric approaches leading to the preparation of (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline.[5]

We envisaged that the *erythro*-4-hydroxy-3-methyl groups of (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline would arise from an asymmetric crotylation[6] to give key intermediate **8** (or **8a**), followed by an amidomercuration–oxidation protocol[7] or a sequence of reactions including Sharpless epoxidation[8] and intramolecular epoxide-opening process[9] (Scheme 2).

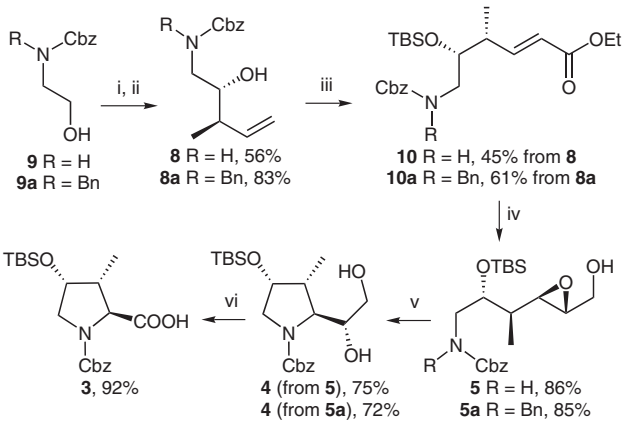


Scheme 2 Retrosynthesis of (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline

From a retrosynthetic viewpoint, the carboxylic acid group in **3** could be masked as a vicinal diol, which leads to compound **4**. Further disconnection at the C2–N bond gives the key precursor epoxide **5**, which in turn could be obtained from alkene **8** (or **8a**). The alkene **8** (or **8a**) can be easily constructed by using Brown's asymmetric crotylation reaction[6] (route A, Scheme 2). Alternatively, **3** could be prepared from the corresponding aldehyde **6**, arising from an epimerization and amidomercuration of alkene **8** (route B, Scheme 2).

The synthesis of **3** commenced with the asymmetric crotylation[6] of aldehydes derived from N-monoprotected and N-bis-protected alcohols **9** and **9a**. TEMPO-mediated oxidation[10] of **9** gave the corresponding aldehyde in 95% yield. This was then reacted with (+)-*B*-(*E*)-crotyldiisopinocampheylborane to give the *anti*-homoallylic alcohol **8** in 56% yield with no discernible trace of the *syn*-stereoisomer by ^{1}H NMR analysis of the crude product. This operation established the absolute stereochemistry at C3 and C4 corresponding to that required for **3**. After conversion of the homoallylic alcohol **8** to its silyl ether, the terminal alkene was cleaved by the action of OsO_4/$NaIO_4$ in the presence of 2,6-lutidine[11] to furnish the corresponding aldehyde, which underwent simultaneous attack by the carbamoyl NH to afford the corresponding cyclic hemiaminal (see Supporting Information). The hemiaminal was then homologated by Wittig olefination to afford α,β-unsaturated ester **10** as the *E*-stereoisomer exclusively. DIBAL-H reduction of **10** afforded the corresponding allylic alcohol, which was subjected to a Sharpless asymmetric epoxidation, using (–)-diisopropyl tartrate as the chiral ligand, to afford the epoxyalcohol **5** in 86% yield over two steps.[8] Removal of the Cbz protecting group by catalytic hydrogenation gave the corresponding free amine, which spontaneously cyclized onto the epoxide by a 5-*exo* process to afford a pyrrolidine derivative that was reprotected in situ with CbzCl to provide **4** in 75% overall yield from the epoxy alcohol **5**.[12] Sodium periodate cleavage of the diol[11] in **4** produced the corresponding aldehyde **6**, which was immediately oxidized under Pinnick conditions[13] to furnish **3** in 92% yield. The overall yield for the synthesis of **3** from **9** was 15%.

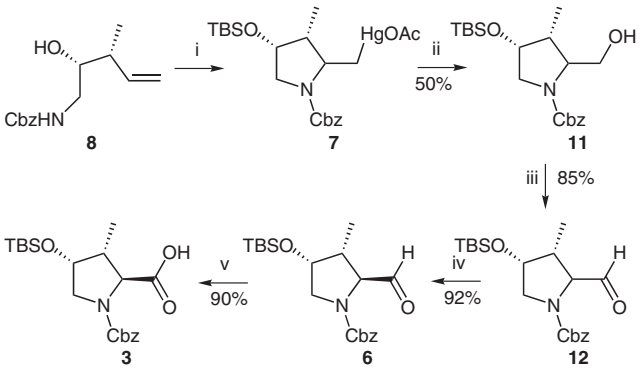
Although this strategy for the synthesis of **3** was successful, the overall yield was not very satisfactory and there was room for improvement. Since the yields for both asymmetric crotylation and Wittig olefination (leading to intermediates **8** and **10**, respectively) were relatively low, we speculated that the unprotected carbamate in **9** might play a critical role in decreasing the yield of these transformations. Therefore, we decided to employ *N*-benzyl-*N*-(benzyloxycarbonyl)ethanolamine (**9a**) as the starting material for the synthesis of **3**. To our delight, asymmetric crotylation of the **9a**-derived aldehyde afforded homoallylic alcohol **8a** in 83% yield. In addition, the transformation of **8a** to **10a**, which involved TBS protection of homoallylic alcohol, sodium periodate cleavage of the diol, and Wittig olefination of the resulting aldehyde, was accomplished in 61% yield over three steps (Scheme 3). The Wittig olefination leading to **10a** was performed at room temperature while the similar reaction leading to **10** needed to be conducted at high temperature. Since simultaneous removal of both Cbz and Bn protecting groups in **5a** with Pd/C as catalyst was very slow, Pearlman's catalyst was employed for the epoxide-opening process to give **4** in 72% yield. Thus, the overall yield for the synthesis of **3** from **9a** was improved to 29%.



Scheme 3 Epoxide-opening approach. *Reagents and conditions:* i, TEMPO, TCCA, CH_2Cl_2, 0 °C; ii, KO*t*-Bu, *n*-BuLi, *trans*-2-butene, (+)-IPC_2BOMe, $BF_3{\cdot}OEt_2$, –100 °C, then H_2O_2, Et_3N, THF; iii, (a) TBSCl, imidazole, DMAP (cat.), DMF; (b) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane–H_2O; (c) Ph_3PCHCO_2Et, benzene, reflux (for **10**) or Ph_3PCHCO_2Et, CH_2Cl_2, r.t. (for **10a**); iv, (a) DIBAL-H, CH_2Cl_2, –78 °C to –20 °C; (b) (–)-DIPT, $(i\text{-PrO})_4Ti$, TBHP, 4 Å MS, CH_2Cl_2, –40 °C; v, (a), H_2, Pd/C, MeOH (from **5**); or H_2, Pearlman's catalyst (from **5a**); (b) CbzCl, $NaHCO_3$, THF–H_2O; vi, (a) $NaIO_4$–SiO_2, CH_2Cl_2; (b) $NaClO_2$, NaH_2PO_4, $MeSO_2NH_2$, *t*-BuOH–H_2O.

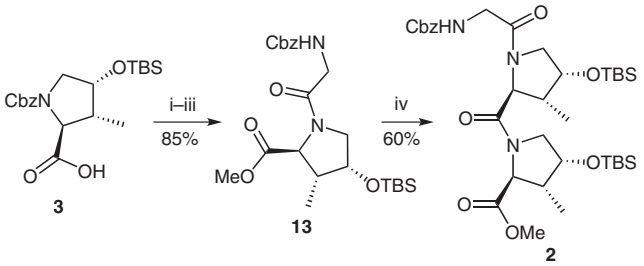
In order to explore a more convenient protocol for the preparation of **3**, we also investigated a synthetic approach based on intramolecular amidomercuration of the TBS-protected intermediate **8**. The rationale behind this decision was supported by the well-known mercury(II)-mediated 5-*exo*-trig cyclization.[7] In addition, we envisaged that the stereochemistry for the stereogenic center adjacent to the aldehyde group in **12** would be determined by the substituents at C3 and C4 of the pyrrolidine ring. Therefore, under basic conditions, the diastereomer with the *syn*-C2 stereogenic center should epimerize to the configuration required for the target molecule.

Thus, after protection of the homoallylic alcohol **8** using *tert*-butyldimethylsilyl chloride, the resulting TBS ether was treated with $Hg(OAc)_2$ in acetonitrile to afford the corresponding pyrrolidine derivative as a mixture of two diastereomers. Subsequent workup under standard conditions[14] and oxidative demercuration of the organomercury adduct in the presence of molecular oxygen afforded the trisubstituted pyrrolidine derivative **11** in 50% yield.[15] Dess–Martin oxidation of the primary alcohol in **11** produced the corresponding aldehyde **12** in 85% yield as a mixture of diastereomers. To our delight, treatment of aldehyde **12** with DBU equalized the diastereomeric mixture of **12** to the thermodynamically more stable isomer in 92% isolated yield with the stereochemistry shown in **6**. Pinnick oxidation[13] of **6** furnished the desired compound **3** in 90% yield (Scheme 4). The overall yield for the synthesis of **3** from **9** of the amidomercuration–oxidation-based protocol was 20%.



Scheme 4 Amidomercuration–oxidation-based approach. *Reagents and conditions:* i, (a) TBSCl, imidazole, DMAP (cat.), DMF; (b) $Hg(OAc)_2$, MeCN; ii, O_2, $NaBH_4$, DMF; iii, Dess–Martin periodinate, CH_2Cl_2; iv, DBU; v, $NaClO_2$, NaH_2PO_4, $MeSO_2NH_2$, *t*-BuOH–H_2O.

With the requisite 4-hydroxy-3-methylproline in hand, the desired tripeptide **2** was readily prepared in good yield via a series of standard transformations including esterification of **3** with diazomethane, hydrogenation of the resulting methyl ester with Pd/C to produce the corresponding free amine, which was coupled with Cbz-protected glycine to afford **13**. Saponification of the methyl ester in **13** to the corresponding acid, followed by coupling with the free amine derived from **3** in the presence of BOPCl produced **2** in 60% yield (Scheme 5).[16]



Scheme 5 Synthesis of fragment **2**. *Reagents and conditions:* i, CH_2N_2, Et_2O; ii, H_2, Pd/C, MeOH; iii, Cbz-Gly-OH, BOPCl, DMF; iv, (a), LiOH, THF–MeOH–H_2O; (b) BOPCl, **3**, DIPEA, DMF.

In summary, we have developed two practical approaches for the synthesis of 4-hydroxy-3-methylproline derivative. A tripeptide fragment based on 4-hydroxy-3-methylproline of scytonemin A has also been successfully prepared. Efforts toward the completion of the total synthesis of scytonemin A are currently under way in our laboratory, and our progress will be disclosed in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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(12) **Procedure for the Synthesis of 4 via Epoxide Opening**
Epoxide **5** (0.65 g, 1.6 mmol) was dissolved in MeOH (10 mL). After a catalytic amount of Pd/C (10%) was added, the reaction was exposed to an atmosphere of H_2 at ambient temperature. The reaction was monitored by TLC. After all starting material was consumed (ca. 2 h), the reaction mixture was stirred for an additional 1 h and then filtered through a pad of Celite. The filter cake was washed with MeOH (10 mL). The combined filtrate and washings were concentrated in vacuo to leave the corresponding amine as an oil, which was dissolved in THF–H_2O (20 mL, 1:1) at 0 °C and treated with $NaHCO_3$ (0.25 g, 3.0 mmol) and CbzCl (0.29 mL, 2.0 mmol). The reaction mixture was stirred at r.t. for 3 h and then concentrated in vacuo. The residue was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel, eluting with EtOAc–hexane (2:3) to give desired product **4** (0.49 g, 75%); $[a]_D^{25}$ –6.6 (*c* 0.70, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.29 (m, 5 H), 5.17 (s, 2 H), 4.17 (d, *J* = 3.3 Hz, 1 H), 4.11 (d, *J* = 9.0 Hz, 1 H), 3.73 (dd, *J* = 4.2, 7.1 Hz, 1 H), 3.61–3.58 (m, 4 H), 3.34 (dd, *J* = 4.1, 11.6 Hz, 1 H), 3.09–3.07 (m, 1 H), 2.18 (dd, *J* = 6.9, 11.5 Hz, 1 H), 1.12 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR (125 MHz, CDCl3): δ = 157.7, 136.3, 128.5 (128.5), 128.2, 128.0 (127.9), 73.4, 72.2, 67.6, 65.7, 62.9, 54.5, 41.4, 25.8 (25.7), 18.0, 13.0, –4.9, –5.0 ppm. ESI-HRMS: *m/z* calcd for $C_{21}H_{36}NO_5Si^+$ $[M + H]^+$: 410.2351; found: 410.2375.

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(15) **Procedure for the Synthesis of 11 via Amidomercuration–Oxidation**
To a stirred solution of compound **8** (0.88 g, 2.40 mmol) in MeCN (20 mL), $Hg(OAc)_2$ (2.26 g, 7.20 mmol) was added. The reaction mixture was refluxed for 2 h and then cooled to r.t. EtOAc (10 mL) and brine (10 mL) were added, and the mixture was stirred at r.t. for a further 1.5 h and filtered to remove the precipitated inorganic byproduct. The filtrate was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give **7** as a colorless foam. In a second reaction vessel, oxygen (O_2) was bubbled into a well-stirred solution of $NaBH_4$ (0.09 g, 2.4 mmol) in DMF (25 mL) at r.t. One hour later, the above intermediate in DMF (25 mL) was slowly added over 2 h, while maintaining the flow of oxygen. Upon completion of addition, the reaction mixture was stirred for additional 2 h and then filtered through a pad of Celite, eluting thoroughly with EtOAc (200 mL). The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (EtOAc–hexane, 3:1) to afford the diastereoisomers **11α** (0.23 g, 26%) and **11β** (0.22 g, 24%).
Analytical Data for 11α
$[\alpha]_D^{25}$ +28.6 (*c* 0.54, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$); δ = 7.37–7.27 (m, 5 H), 5.22–5.09 (m, 2 H), 4.24–4.02 (m, 2 H), 3.94–3.79 (m, 2 H), 3.72–3.66 (m, 1 H), 3.60–3.55 (m, 1 H), 3.52–3.42 (m, 1 H), 2.46–2.33 (m, 1 H), 1.07 (1.05) (d, *J* = 7.4 Hz, 3 H), 0.92 (0.91) (s, 9 H), 0.14 (0.09) (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (154.9), 136.7, 128.5, 128.0, 127.9, 73.4 (72.8), 67.1, 62.8 (61.9), 61.5 (59.8), 56.1 (55.4), 41.4 (40.7), 25.7, 18.0, 9.9 (9.7), –4.8, –5.1 ppm. ESI-HRMS: *m/z* calcd for $C_{20}H_{34}NO_4Si^+$ $[M + H]^+$: 380.2252; found: 380.2268.
Analytical Data for 11β
$[\alpha]_D^{25}$ –2.0 (*c* 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 5 H), 5.35–5.10 (m, 2 H), 4.85 (br, 1 H) 4.05 (br, 1 H), 3.82–3.80 (m, 1 H), 3.70–3.66 (m, 1 H), 3.62–3.58 (m, 2 H), 3.38 (dd, *J* = 3.0, 13.4 Hz, 1 H), 1.84–1.77 (m, 1 H), 1.06 (d, *J* = 6.7 Hz, 3 H), 0.87 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4, 136.4, 128.5, 128.0, 127.8, 72.3, 67.3, 65.9, 65.6, 55.6, 41.4, 25.7, 18.0, 11.9, –4.8, –5.0 ppm. ESI-HRMS: *m/z* calcd for $C_{20}H_{34}NO_4Si^+$ $[M + H]^+$: 380.2252; found: 380.2264.

(16) See Supporting Information.