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Towards solomonamide A: asymmetric synthesis of the unusual γ-amino acid part

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ABSTRACT

Fully functional and differentially protected synthesis of the unusual γ-amino acid part of the very powerful anti-inflammatory cyclic peptide solomonamide A has been achieved in a straight forward manner in good yields.

Novel bioactive metabolites are essential components in drug discovery. Undoubtedly marine sponges are occupying the front slot in providing interesting natural products and scaffolds with very diverse biological profiles.[1] Very recently, Zampella and coworkers have reported the isolation of new octacyclopeptides perthamides C and D[2] from *Theonella Swinhoei*. Further investigations on *Theoneela Swinhoei* by the same group provided two minor peptide derivatives solomonamide A (**1**) and B (**2**, Fig. 1).[3] The solomonamide A (**1**) has exhibited anti-inflammatory activity at 100 μg/kg in animal models. The extensive degradation and spectral studies have revealed that solomonamide A comprises of an unprecedented 4-amino(2′-amino-4′-hydroxy phenyl)-3,5-dihydroxy-2-methyl-6-oxohexanoic acid (ADMOA) besides the proteinogenic alanine and glycine as a 15-membered cyclic tripeptide.

While no synthetic efforts are reported in the literature to date towards solomonamide A, the partial synthesis of solomonamide B is recently published.[4] Our group is engaged in the synthesis of marine natural cyclic peptides as part of a programme towards building repository of natural products.[5] Herein, we describe the first synthesis of fully functionalized and appropriately protected unusual amino acid framework **4** with excellent stereo control in a convergent fashion starting from commercially available (*R*)-Roche ester via chiral epoxide **10** and amino aldehyde **6** (Scheme 1).

With this strategy as the backdrop, we embarked upon the synthesis of **4** wherein, the precursor compound **7** was synthesized from (*R*)-Roche ester following the literature procedure.[6] The DIBAL-H reduction of ester **7** and homologation of the rather unstable aldehyde (degradation observed within 1 h) under Horner–Emmons conditions[7] using KH as a base and 18-crown-6 as phase transfer catalyst provided *Z*-olefinic ester **8** in 72% yield as the major isomer (The minor *E*-isomer was separated by column chromatography). Further, the compound **8** was reduced with DIBAL-H to generate the *Z*-allyl alcohol **9** which underwent a facile epoxidation[8] with *m*-CPBA in CH_2Cl_2 at −10 °C to provide epoxy alcohol **10** with excellent diastereoselectivity (97:3).[9] The epoxy alcohol **10** after purification when exposed to NaN_3 in the presence of trimethyl borate allowed a smooth regioselective epoxide cleavage[10] to yield the azido diol **11**. The unwanted 1,2-diol (1,3-opening) was destroyed by the addition of $NaIO_4$ to the reaction mixture. Disilylation of **10** with TBSOTf was rather easily accomplished to furnish **12** in 84% yield. The azido group in **12** was reduced under Staudinger conditions[11] and the resultant

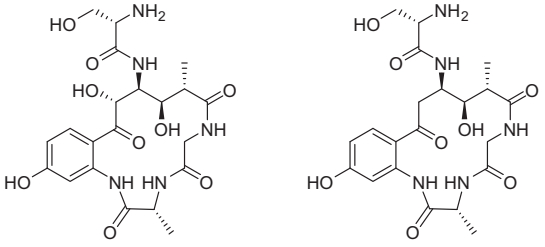

Figure 1. Structures of **1** and **2**.

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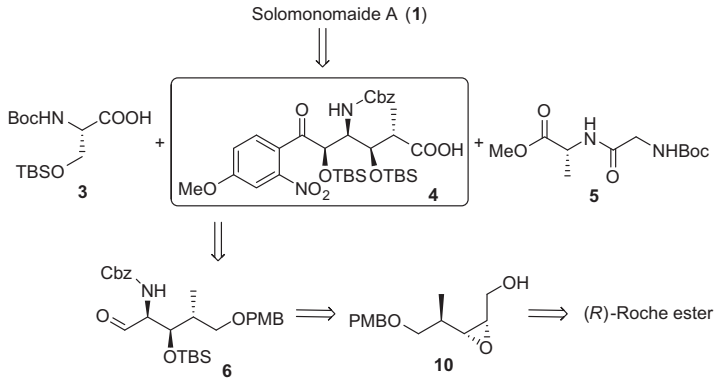
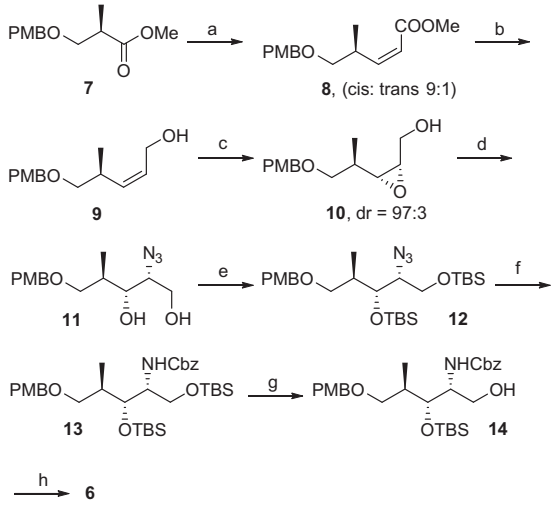
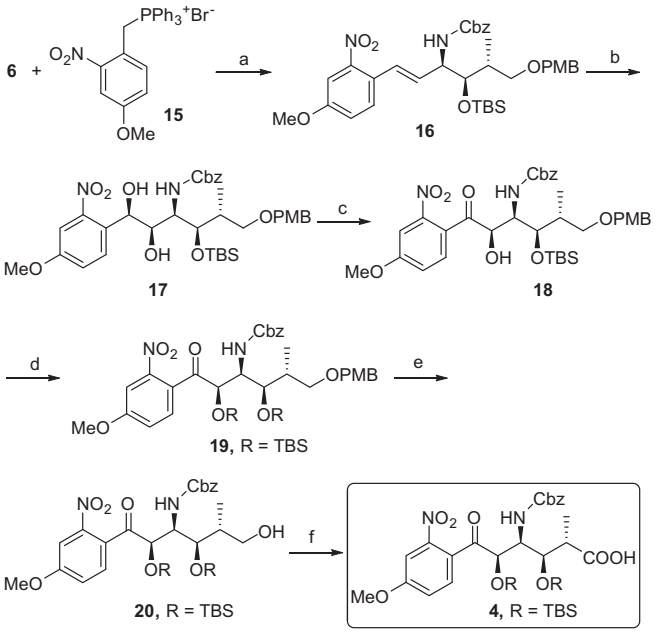


Scheme 1. Retrosynthesis of solomonamide A.



Scheme 2. Reagents and conditions: (a) DIBAL-H, hexane, −78 °C, 10 min followed by triphenylphosphonoacetate, KH, 18-crown-6, THF, −78 °C, 2 h, 72% (for two steps); (b) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 78%; (c) *m*-CPBA, CH_2Cl_2, −10 °C, 6 h, 88%; (d) NaN_3, $B(OMe)_3$, DMF, 50 °C, 15 h followed by $NaIO_4$, THF/H_2O (8:2), 1 h, 84%; (e) TBSOTf, DIPEA, CH_2Cl_2, −78 °C, 3 h, 84%; (f) (i) triphenyl phosphine, benzene/H_2O, 60 °C, 24 h; (ii) CbzCl, Et_3N, CH_2Cl_2, rt, 12 h, 87% (for two steps); (g) *p*TSA, MeOH, 0 °C, 1 h, 80%; (h) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 90%.



Scheme 3. Reagents and conditions: (a) NaH, CH_2Cl_2, rt, 12 h, 83%; (b) AD-mix-β, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C, 48 h, 74%; (c) DMP, CH_2Cl_2, rt, 2 h, 83%; (d) TBSOTf, DIPEA, CH_2Cl_2, 0 °C, 3 h, 76%; (e) DDQ, CH_2Cl_2/pH buffer (10:1), 0 °C, 4 h, 85%; (f) BAIB, TEMPO, CH_3CN/pH buffer (1:1), rt, 4 h, 78%.

amine was quickly protected as benzyl carbamate **13** in 87% overall yield for two steps. The selective primary desilylation in **13** with *p*TSA in methanol furnished **14**, which underwent oxidation to aldehyde **6** using Dess–Martin periodinane conditions (Scheme 2).

After constructing the aliphatic chiral component, the next task was to stitch the aryl group which was accomplished by a Wittig protocol.[12] Thus, the aldehyde **6** was exposed to the Wittig salt **15**[12] with NaH as a base to yield the styrene derivative **16** as a separable *E*/*Z* mixture (70:30).[13] The major *E*-isomer **16** was obtained by careful chromatography and was subjected to sharpless asymmetric dihydroxylation[14] using AD-mix-β to install the diol group. The resultant diol **17** was subjected to controlled oxidation using Dess–Martin periodinane in dichloromethane to yield compound **18** wherein the benzylic hydroxy group was selectively oxidized. The free hydroxyl group in **18** was silylated to **19** and oxidative cleavage of PMB ether using DDQ[15] provided the primary alcohol **20**. Following, Epp and Widlanski conditions[16] (BAIB, TEMPO, CH_3CN) under buffer medium resulted in the fully functionalized and appropriately protected unusual amino acid precursor **4** in 78% yield (Scheme 3). This compound is fully characterized by ^1H and ^{13}C NMR, HRMS and other supporting spectral data[17].

In conclusion, we have used robust and easily accessible chemicals and reactions viz (*R*)-Roche ester, sharpless asymmetric dihydroxylation and Wittig reaction as key components in the synthesis of the unusual γ-amino acid fragment of solomonamide A. Further work towards total synthesis is in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.032.

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17. *Spectral data for target compound (**4**):* $[\alpha]_D^{25} = +82.4$ ($c = 0.94$, $CHCl_3$); IR (neat): ν_{max} 3440, 2934, 2858, 1715, 1535, 1251, 1125, 837, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (d, $J = 8.4$ Hz, 1H), 7.41–7.31 (m, 6H), 7.08–7.02 (dd, $J = 2.4$, 8.6 Hz, 1H), 5.12 (d, $J = 9.8$ Hz, 1H), 5.07 (s, 2H), 4.72 (d, $J = 4.9$ Hz, 1H), 4.27–4.18 (m, 1H), 4.03 (t, $J = 4.7$ Hz, 1H), 3.89 (s, 3H), 2.75–2.65 (m, 1H), 1.13 (d, $J = 7.1$ Hz, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.11–0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.4, 177.8, 161.8, 155.9, 149.4, 136.4, 132.1, 128.4, 128.2, 128.1, 124.4, 118.0, 109.8, 72.2, 67.0, 60.3, 56.0, 55.1, 43.6, 29.6, 25.8, 25.7, 13.5, −4.0, −4.5, −4.6, −5.0; HRMS (ESI): m/z calcd for $C_{34}H_{52}N_2NaO_{10}Si_2$: $[M+Na]^+$ 727.3054, found 727.3052.