Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 47 (2006) 7307–7309
Tetrahedron Letters

Synthesis of protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid, a constituent of callipeltins A and D☆

S. Chandrasekhar,* M. Srinivasa Reddy, G. S. Kiranbabu and A. Sai Krishna Murthy

Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 22 June 2006; revised 31 July 2006; accepted 10 August 2006
Available online 1 September 2006

Abstract—An efficient synthesis of protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxy heptanoic acid, a constituent of the depsipeptides, callipeltins A and D from L-ascorbic acid is described.
© 2006 Elsevier Ltd. All rights reserved.

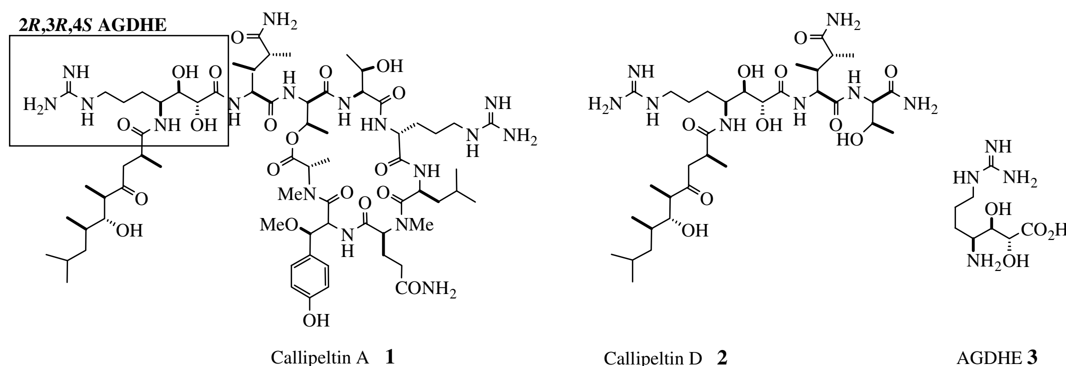
Cyclic depsipeptides have emerged as an important class of biologically active molecules.[1] The novel depsipeptide callipeltin A was first isolated from the marine sponge *Callipelta* sp. by Zempella et al.[2] and later isolated from *Latruncula* sp. along with the truncated open chain derivative callipeltin D.[3] Callipeltin A has shown potent antifungal and anti HIV activities, as well as cytotoxicity against several human carcinoma cell lines.[4] Recently, it was also found to be a selective and powerful inhibitor of the Na/Ca cardiac exchanger and a positive inotropic agent in the atria of guinea pig.[5]

The (2*R*,3*R*,4*S*)-4-amido-7-guanidino-2,3-dihydroxy heptanoic acid (AGDHE) chain is a key fragment in callipeltin A and is found to be responsible for the anti-HIV activity. Recently, a few reports have appeared on the synthesis of this fragment.[6,7] Herein, we report the synthesis of the AGDHE fragment starting from L-ascorbic acid in a more efficient manner with less synthetic steps.

The retrosynthetic analysis of the AGDHE fragment of callipeltin A is described in Scheme 1.

The synthesis of the protected unusual amino acid **19** began from the known optically pure aldehyde **5**, which can be obtained from the readily available L-ascorbic acid **4**[8] (Scheme 2).

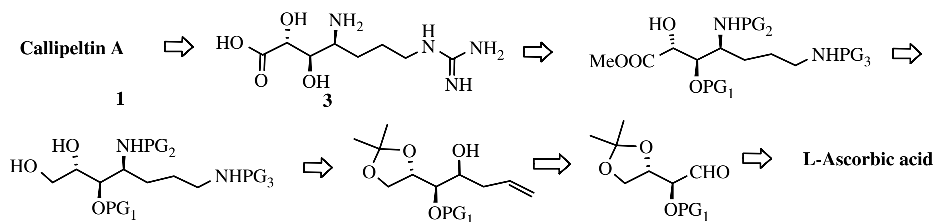
Aldehyde **5** was treated with allylbromide and zinc powder[9] to furnish homoallylic alcohol **6** as an inseparable diastereomeric mixture with 1:5 *syn:anti*



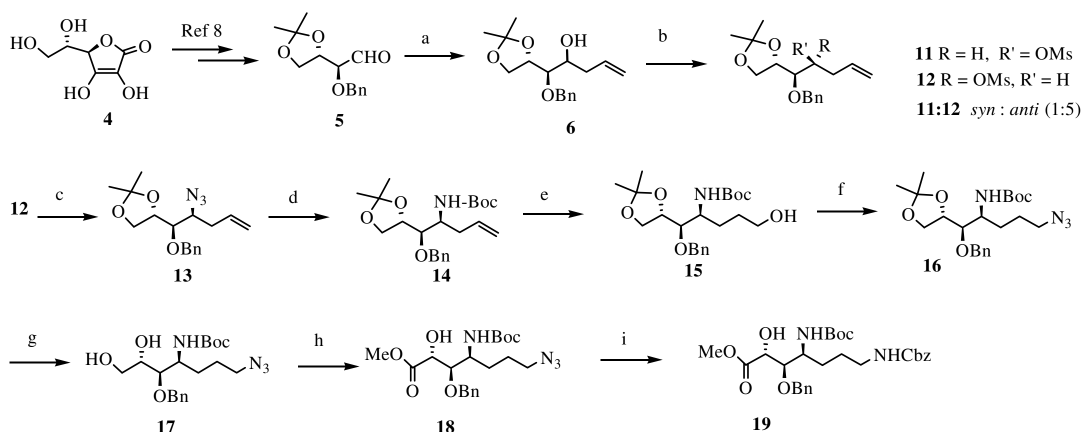
Callipeltin A **1** Callipeltin D **2** AGDHE **3**

Keywords: Callipeltin A; Ascorbic acid; Unusual amino acid.
☆ IICT Communication No.: 060618.
* Corresponding author. Tel.: +91 40 27193434; fax: +91 40 27160512; e-mail: srivaric@iict.res.in

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.08.026



Scheme 1. Retrosynthesis of the AGDHE fragment of callipeltins A and D.



Scheme 2. Reagents and conditions: (a) Zn, allyl bromide, aq NH_4Cl, THF, 0 °C, 85%; (b) MsCl, TEA, CH_2Cl_2, 92%; (c) NaN_3, DMF, 80 °C, 85%; (d) (i) $LiAlH_4$, THF, 0 °C, (ii) $(Boc)_2O$, NaOH, THF, 0 °C, 90%; (e) BH_3–DMS, NaOH, H_2O_2, THF, 0 °C, 80%; (f) (i) TsCl, TEA, CH_2Cl_2, (ii) NaN_3, DMF 80 °C, 85%; (g) 0.8% H_2SO_4, MeOH, 90%; (h) (i) TEMPO, NCS, TBACl, pH = 8.6 CH_2Cl_2, (ii) $NaClO_2$, NaH_2PO_4, H_2O_2, CH_3CN, (iii) CH_2N_2, dry ether, 60%; (i) (i) Pd–$CaCO_3$, H_2, EtOAc, (ii) Cbz-Cl, DIPEA, CH_2Cl_2, 90%.

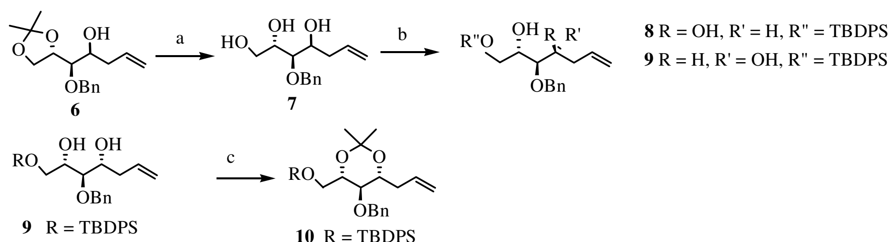
diastereoselectivity (determined by ^{1}H NMR). The relative stereochemistry of the new stereogenic center in the major isomer was determined by a short deprotection–protection protocol (Scheme 3).

The deprotection of the 1,2-acetonoide in homoallylic alcohol **6** and protection of the primary hydroxy group as its TBDPS ether was achieved very easily. At this stage, the two diastereomers **8** and **9** were separated by column chromatography. The major isomer **9** was then protected as its isopropylidine derivative using 2,2-DMP to yield compound **10**.

The ^{13}C NMR spectrum of the acetonide derivative **10** showed that the gem dimethyls resonate at 19.4 and 29.3 ppm and the ketal carbon at 98.2 ppm proving the *syn* relationship between C1–OH and C3–OH with the chair conformation.[10] These values are in accordance with the literature.

The diastereomeric mixture of the homoallylic alcohols **6** was then esterified with methanesulfonyl chloride to give crude mesylates **11** and **12** in 92% yield. The major **12** and minor **11** diastereomers were easily separated by standard silica gel column chromatography and mesylate **12** was then converted to its azide derivative **13** by treatment with NaN_3 in DMF for 12 h. The reduction of azide **13** using $LiAlH_4$ and in situ protection with $(Boc)_2O$ yielded *N*-Boc derivative **14**.

The hydroboration of the *N*-Boc derivative **14** with $BH_3{\cdot}DMS$ furnished the primary alcohol **15**, which was then converted to azide **16** via the tosylate derivative. The acetonide group of **16** was then cleaved to yield diol **17** and the primary alcohol in diol **17** was selectively oxidized[11a] using TEMPO/NCS in the presence of TBACl to furnish the hydroxy-aldehyde derivative, which was immediately treated with $NaClO_2$, NaH_2PO_4, H_2O_2 in acetonitrile to give the corresponding acid,[11b]



Scheme 3. Reagents and conditions: (a) 0.8% H_2SO_4, MeOH, 90%; (b) TBDPSCl, imidazole, CH_2Cl_2, 92%; (c) 2,2-DMP, CSA, CH_2Cl_2, 95%.

which was esterified as its methyl ester **18** using ethereal diazomethane.

Finally, the azide in **18** was reduced using Pd–$CaCO_3$/H_2 to give the amine, which was protected as its Cbz derivative using CbzCl in the presence of DIPEA to furnish the protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid **19** in acceptable yield, which was confirmed by routine spectral analyses.[12]

In conclusion, we have developed an efficient synthetic approach for the preparation of a protected form of the unusual amino acid fragment **19** of callipeltins A and D. It is to be noted that the protected amino acid fragment of callipeltin A was achieved in fewer steps in the current approach, when compared to our earlier approach.[6a]

Acknowledgment

M.S.R. and G.S.K. thank CSIR, New Delhi for the financial support in the form of fellowships.

References and notes

1. Ireland, C. M.; Molinski, T. F.; Roll, D. M.; Zabriskie, T. M.; McKee, T. C.; Swersey, J. C.; Foster, M. P. In *Bioorganic Marine Chemistry*; Scheuer, P. J., Ed.; Springer: Berlin, Heidelberg, 1989; pp 1–46.
2. Zampella, A.; Valeria D'Auria, M.; Gomez Paloma, L. *J. Am. Chem. Soc.* **1996**, *118*, 6202–6209.
3. Zampella, A.; Randazzo, A.; Borbone, N.; Luciani, S.; Trevisi, L.; Debitus, C.; D'Auria, M. V. *Tetrahedron Lett.* **2002**, *43*, 6163–6166.
4. D'Auria, M. V.; Zampella, A.; Paloma, L. G.; Minale, L.; Debitus, C.; Roussakis, C.; Le Bert, V. *Tetrahedron* **1996**, *52*, 9589–9596.
5. Trevisi, L.; Bova, S.; Cargnelli, G.; Danieli-Betto, D.; Floreani, M.; Germinario, E.; D'Auria, M. V.; Luciani, S. *Biochem. Biophys. Res. Commun.* **2000**, *279*, 219–222.
6. (a) Chandrasekhar, S.; Ramachander, T.; Venkateswara Rao, B. *Tetrahedron: Asymmetry* **2001**, *12*, 2315–2321; (b) Ravi Kumar, A.; Venkateswara Rao, B. *Tetrahedron Lett.* **2003**, *44*, 5645–5647.
7. (a) Thoen, J. C.; Morales-Ramos, A.; Lipton, M. A. *Org. Lett.* **2002**, *4*, 4455–4458; (b) Jongho, J. H.; Suk-Koo, H.; Joon, S. O.; Young, G. K. *J. Org. Chem.* **2006**, *71*, 3310–3313.
8. Ermolenko, L.; Sasaki, N. A. *J. Org. Chem.* **2006**, *71*, 693–703.
9. Chan, T. H.; Li, C. J. *Can. J. Chem.* **1992**, *70*, 2726–2729.
10. (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100; (c) Rychnovsky, S. D.; Roger, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9–17.
11. (a) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J. L. *J. Org. Chem.* **1996**, *61*, 7452–7454; (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567–569.
12. The spectral data for selected compounds: compound **13** $[\alpha]_D^{25}$ −15.8 (*c* 1.0, $CHCl_3$). IR (KBr): 3414, 2986, 2111, 1618, 1375, 1217, 1073, and 769 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.38–7.23 (m, 5H), 5.83–5.68 (m, 1H), 5.18–5.10 (m, 2H), 4.74 (d, $J = 11.3$ Hz, 1H), 4.64 (d, $J = 11.3$ Hz, 1H), 4.14 (q, $J = 6.04$, 1H), 4.04 (dd, $J = 8.30$, 6.04 Hz, 1H), 3.88 (dd, $J = 8.30$, 6.04 Hz, 1H), 3.60 (dd, $J = 5.28$, 2.28 Hz, 1H), 3.26 (dt, $J = 6.79$, 3.02 Hz, 1H), 2.57–2.36 (m, 2H), 1.38 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 137.7, 133.6, 128.4, 127.8, 127.6, 118.5, 108.8, 80.5, 74.9, 66.2, 61.7, 34.8, 23.5, and 24.2. ESI-MS: *m*/*z* 340 $(M+Na)^+$. Compound **19**: $[\alpha]_D^{25}$ −31.2 (*c* 0.4 $CHCl_3$). IR (KBr): 3418, 2928, 1704, 1364, 1248, 1165, 788 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.42–7.26 (m, 10H), 5.09 (s, 2H), 4.82–4.70 (m, 2H), 4.59 (d, $J = 10.6$ Hz, 1H), 4.46 (d, $J = 10.6$ Hz, 1H), 4.12 (d, $J = 8.30$ Hz, 1H), 3.96–3.85 (m, 1H), 3.77 (s, 3H), 3.64 (d, $J = 8.30$ Hz, 1H), 3.24–3.09 (m, 3H), 1.56–1.37 (m, 13H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 173.0, 156.9, 156.4, 137.4, 136.5, 128.5, 128.2, 128.1, 81.6, 80.2, 74.5, 71.0, 66.6, 52.4, 50.7, 40.6, 30.3, 29.5, 28.3, and 26.8. ESI-MS: *m*/*z* 553 $(M+Na)^+$, 530 $(M)^+$.