CHEMISTRY LETTERS, pp. 2385-2388 1992.

Stereocontrolled Total Synthesis of 9(R)-N-BOC-Ahda Methyl Ester

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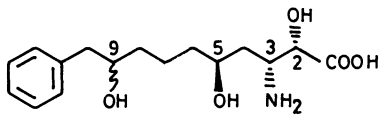
An efficient convergent route to the first total synthesis of 9(R)-N-BOC-Ahda methyl ester, in optically pure form, is described.

A unique C_{16} amino acid (2S,3R,5S)-3-amino-2,5,9-trihydroxy-10-phenyldecanoic acid (Ahda, **1**) is a major component of potent calcium antagonist scytonemin A (**2**), a novel cyclic peptide isolated from the cultured cyanophyte Scytonema sp. (strain U-3-3).[1] Biogenetically Ahda appears to be related to 3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda) present in many closely related toxins produced by cyanobacteria.[2] The C9 carbon in the Ahda unit is the only asymmetric center in the entire scytonemin A molecule of unknown chirality. Therefore, a stereocontrolled total synthesis of this unusual β-amino acid to establish its C9 configuration is very much essential, not only to understand its biogenesis, but also to attempt the synthesis of the parent cyclic peptide for further biological investigations.



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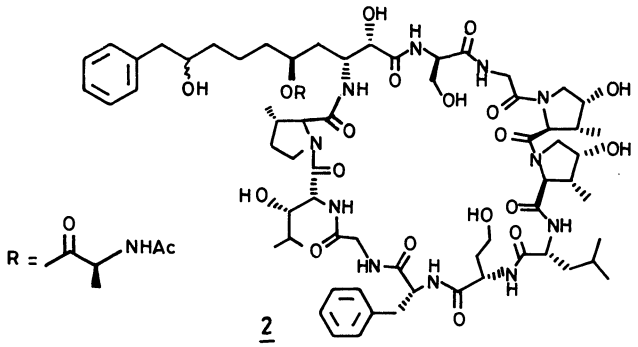

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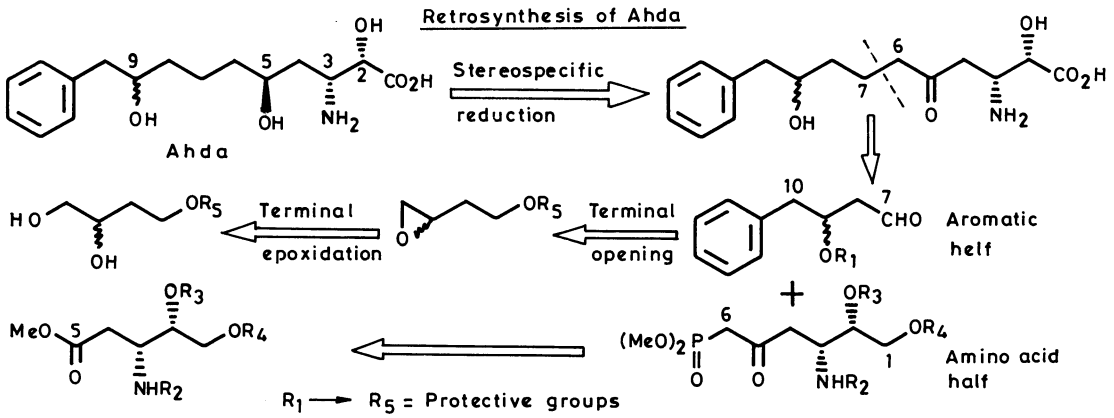
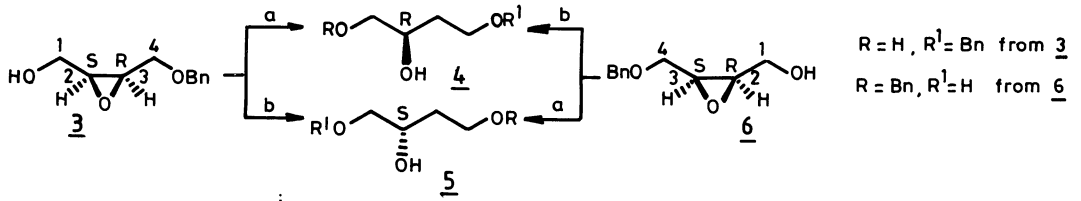
The presence of four chiral centers in Ahda makes its total synthesis a challenging task. Herein, we report the first total synthesis of 9(R)-N-BOC-Ahda methyl ester. The scheme outlined here can give rise to Ahda with either 9(R) or 9(S) configuration, whichever is desired, in enantiomerically pure form. Retrosynthetically Ahda can be divided into two halves: the left aromatic half from C7 to C10 and the right amino acid half from C1 to C6.

In order to establish the stereochemistry at C9 position it was felt necessary to have access to both stereoisomers of the aromatic half which logically can be constructed following simple steps from 4-hydroxy protected butane-1,2,4-triol of requisite chirality. Keeping this in mind, we have developed a simple and practical approach which provided both the stereoisomers of the protected triol from a common homochiral (2S,3R)-epoxy alcohol **3** (Scheme 1), a versatile synthon prepared by Sharpless asymmetric epoxidation of 4-benzyloxy-cis-2-buten-1-ol



using natural diethyl tartrate.[3] Lithium borohydride in presence of $Ti(O^iPr)_4$[4] opened **3** predominently at C3 position giving **4** as the major product (9:1 of **4**:**5**),[5] while Red-Al led exclusively to the C2 opened product **5**.[6] On the other hand, with just the choice of reagents reversed, the (2R,3S)-epoxide, obtained by using unnatural diethyl tartrate in Sharpless epoxidation, provided the same isomeric alcohols.[7]

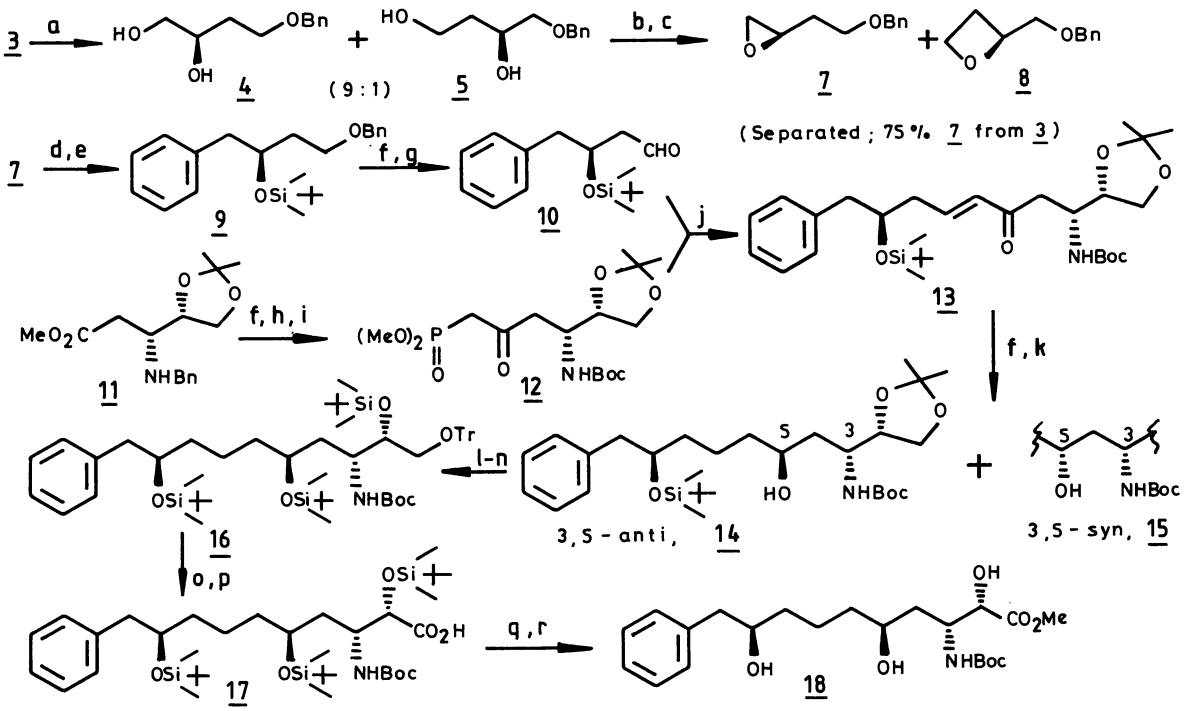


a) $LiBH_4$ (2.0 equiv.), $Ti(O^iPr)_4$ (1.7 equiv.), THF, 0 °C, 6 h, 96% (9:1 mixture of **4**:**5** from **3**, or **5**:**4** from **6**); b) Red-Al (2.0 equiv.), THF, -20 °C, 2 h, 98% (single product).

Scheme 1.

This mixture of products obtained by $LiBH_4/Ti(O^iPr)_4$ opening of epoxide **3** was treated, as such, with $TsCl/Et_3N$ in DCM (Scheme 2). The inseparable mixture of primary tosylated products on treatment with NaH in THF gave the terminal epoxide **7**[8] as the major product (75% from **3**) which could be easily separated, by chromatography, from the four membered oxetane **8** given by primary tosylated 1,3-diol. Opening of **7** with PhMgBr followed by silylation gave the R-stereoisomer **9**. Finally, debenzylation and oxidation led to the desired aromatic half **10**.[8]

The correct positioning of the requisite functional groups in the five carbon unit **11**, obtained easily in large quantities from D-mannitol in four simple steps,[9] qualified it as the most ideal precursor for the amino acid half of Ahda. Extension by one more carbon was achieved by converting it to the ketophosphonate **12**,[8] ready to be coupled with the other half **10**. This was done following Masamune's procedure[10] to build the basic framework of Ahda **13**. Reduction of the conjugated double bond followed by that of the 5-keto function with $NaBH_4$/MeOH led to a 3:2 mixture[11] of 3,5-anti and 3,5-syn products, **14** and **15** respectively,[12] which were separated easily by standard silica gel column chromatography. The desired 3,5-anti product **14**[8] on routine functional group manipulations provided the primary-O-tritylated intermediate **16**.[8] Detritylation of **16** followed by oxidation of the primary hydroxyl to carboxylic function with pyridinium dichromate (PDC) in DMF[13] furnished the tri-O-silylated-N-BOC-Ahda **17**.[8,14] Finally, esterification and the subsequent deprotection of all silylethers using p-toluene sulfonic acid (cat.) in dry methanol gave the desired 9(R)-N-BOC-Ahda methyl ester **18**.[14]



a) Same as a) in Scheme 1; b) p-TsCl (1.2 equiv.), Et_3N (2.0 equiv.), DMAP (0.4 equiv.), CH_2Cl_2, rt, 12 h, 89%; c) NaH (2.0 equiv.), THF, rt, 98%; d) PhMgBr (1.3 equiv.), THF, rt, 15 min, 92%; e) TBDMSOTf (1.2 equiv.), 2,6-lutidine (2.4 equiv.), CH_2Cl_2, 0 °C, 5 min, 94%; f) H_2, Pd/C (10%), MeOH, rt, 8 h, 96%; g) PDC (2.5 equiv.), 4Å MS, CH_2Cl_2, rt, 2.5 h, 70%; h) $(BOC)_2O$ (1.2 equiv.), Et_3N (1.5 equiv.), CH_2Cl_2, rt, 0.5h, 93%, i) $CH_3PO(OCH_3)_2$, (2.5 equiv.), n-BuLi (2.5 equiv.), THF, -78 °C, 2.5 h, 88%; j) LiCl (1.2 equiv.), DBU (1.0 equiv.), CH_3CN, rt, 5 h, 72%; k) $NaBH_4$ (2.0 equiv.), MeOH, rt, 5 min, 96%; l) p-TsOH (0.2 equiv.), MeOH, rt, 0.5 h, 84%; m) TrCl (1.5 equiv.), Et_3N (2.0 equiv.), DMAP (0.4 equiv.), DMF, rt, 20 h, 74%; n) TBDMSOTf (3.4 equiv.), 2,6-lutidine (6.0 equiv.), CH_2Cl_2, 0 °C, 5 min, 80%; o) p-TsOH (0.1 equiv.), $CHCl_3$-MeOH (1:1), rt, 2 h, 86%; p) PDC (9.0 equiv.), DMF, rt, 24 h, 70%; q) CH_2N_2, Et_2O, 98%; r) p-TsOH (0.2 equiv.), MeOH, rt, 6 h, 96%.

Scheme 2.

The short and practical route described here will enable one to synthesize Ahda easily in multigram quantities in stereocontrolled manner.

We thank Dr A V Rama Rao for his encouragement and keen interest.

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7) Hydrogenation of **4** in presence of Pd/C provided R-butanetriol readily.

8) Satisfactory NMR, Mass and IR spectra were obtained for this compound.

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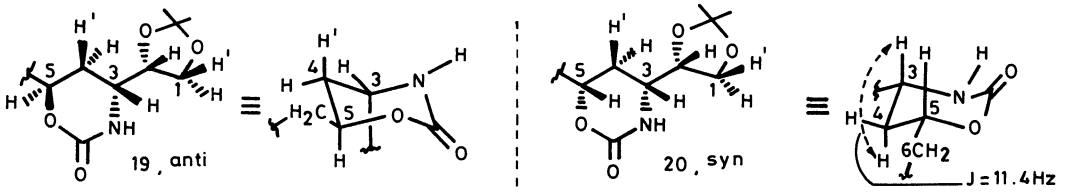
11) Use of "anti-selective" hydride reagents like $NaBH(OAc)_3$ or $(Me_4N)BH(OAc)_3$ did not give any better selectivity. K-selectride gave mainly syn-product **15**. See D.A. Evans, J.A.G. Prunet, E.M. Carreira, and A.B. Charette, J. Org. Chem., 56, 741 (1991).

12) The stereochemistry at the reduced center C5 was determined by ^1H NOE difference spectroscopy. For this purpose both compounds **14** and **15** were converted into their corresponding cyclic carbamates **19** and **20**, respectively. In case of **20** irradiation of the signal of C3-H caused significant enhancement of C5-H resonance, along with the enhancements of signals due to NH, C4-H', C2-H, and C1-H', confirming syn relationship between C3-H and C5-H. Whereas for **19** irradiation of C3-H peak enhanced only NH, C4-H', C2-H, and C1-H' resonances and there was no enhancement of C5-H signal supporting its anti relationship with C3-H; In the ^1H NMR of **20** ($CDCl_3$, 400 MHz) the signal for C3-H showed an eight line pattern at δ 3.38 with J = 4.7, 8.2, and 11.4 Hz. The 11.4 Hz coupling constant confirms its axial position in a six membered chair in which the C5-H also occupies an axial position. The signal for C3-H in **19** ($CDCl_3$, 400 MHz), on the other hand, was very different and showed only a broad dd at the same place with J = 6.3 and 12.5 Hz suggesting its equatorial position having very negligible diequatorial coupling. Careful investigation revealed that the large coupling was with C2-H.



13) E.J. Corey and G. Schmidt, Tetrahedron Lett., 20, 399 (1979).

14) **17:** ^1H NMR (CD_3OD), 400 MHz): δ 7.18-7.36 (m, 5H, aromatic), 4.22 (dd, J=10.8 and 2.7 Hz, 1H, H3), 3.85-4.00 (m, 3H, H2, H5 and H9), 2.78 (dd, J=13.3 and 5.6 Hz, 1H, PhCH), 2.72 (dd, J=13.3 and 7.1 Hz, 1H, PhCH), 1.94 (ddd, J=2.7, 9.0 and 13.5 Hz, 1H, H4'), 1.72 (ddd, J=2.4, 10.8 and 13.5 Hz, 1H, H4), 1.28-1.64 (m, 6H, CH_2), 1.5 (s, 9H, BOC), 0.96, 0.95 and 0.89 (three s, 27H, Si^tBu), 0.12, 0.11, 0.10, 0.012 and -0.18 (singlets, 18H, CH_3). **18:** IR ($CHCl_3$): 1750, 1693 cm^{-1}; $[\alpha]_D$ +3.43 (c 0.32, $CHCl_3$); MS (CI, MeOH): m/z 394 (M^+-OCH_3); ^1H NMR ($CDCl_3$, 200 MHz) : δ 7.15-7.40 (m, 5H, aromatic), 5.4 (d, J=8.4 Hz, 1H, NH), 5.05 (m, 1H, H3), 4.3-4.5 (m, 2H, H2 and H5), 3.7-3.9 (m, 1H, H9), 3.72 (s, 3H, OCH_3), 2.81 (dd, J=4.2 and 13.3 Hz, 1H, PhCH), 2.63 (dd, J=8.3 and 13.3 Hz, 1H, PhCH), 1.4-1.9 (m, 8H, CH_2), 1.48 (s, 9H, ^tBu).

(Received August 5, 1992)