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A New Stereoselective Route to (2*S*, 3*S*, 8*S*, 9*S*, 4*E*, 6*E*)-3-Amino-9-methoxy-2, 6, 8-trimethyl-10-phenyldeca-4, 6-dienoic acid (Adda)

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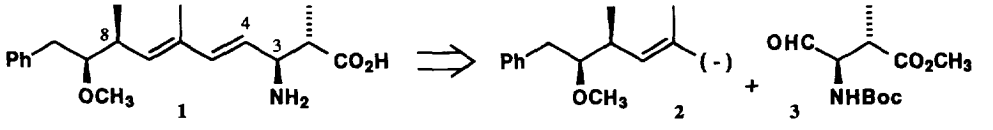
Abstract: *N*-Boc-Adda has been prepared in 15 steps and 9% overall yield from the readily available alcohol, 3-pentyne-2-ol, employing a route that includes two Claisen rearrangements.

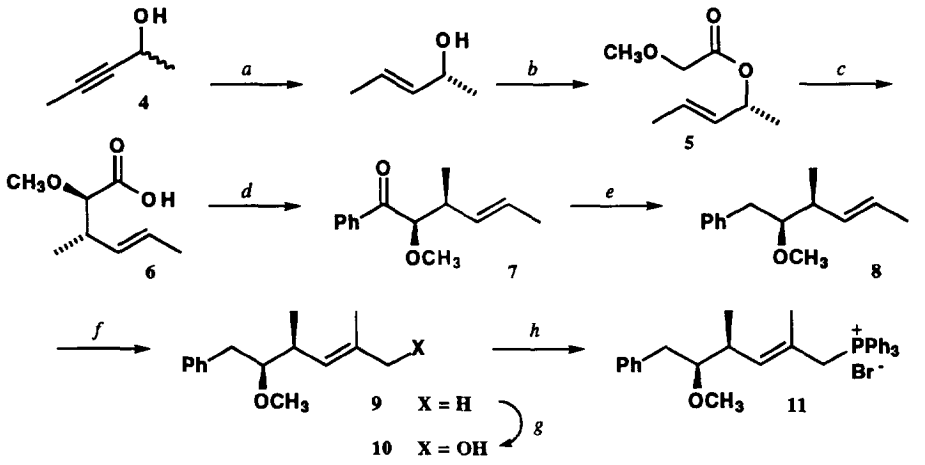
The amino acid (2*S*, 3*S*, 8*S*, 9*S*, 4*E*, 6*E*)-3-amino-9-methoxy-2, 6, 8-trimethyl-10-phenyldeca-4, 6-dienoic acid (Adda, **1**)[1] is a component of the hepatotoxic cyclic peptides called microcystins,[2] as well as the related pentapeptides nodularin[3] and motuporin.[4] The stereochemical complexity of this amino acid, and interest in studying the biochemistry and structure-function relationships of these natural products, have stimulated efforts by several groups to prepare Adda stereoselectively and in high yield.[5-8] The preferred synthetic approach involves late construction of the 4, 5- double bond enabling assembly of the two desired fragments (**2**, **3**; Scheme **1**) from a common precursor. In previous syntheses of Adda,[5-8] the relative and absolute stereochemistry has been established either using an amino acid chiron such as aspartate or threonine, or *via* well-established methods for introducing asymmetry, such as the Evan's aldol procedure or the Sharpless epoxidation. Prompted by the recent report of a total synthesis of motuporin,[8] we describe here a new synthetic route to Adda which employs as starting precursor the propargylic alcohol 3-pentyne-2-ol (**4**, Scheme **2**).



Scheme **1**. The preferred retrosynthetic approach to Adda

Racemic 3-pentyne-2-ol is commercially available and may be resolved as described.[9] Reduction of the (*R*)-alcohol with sodium in liquid ammonia, followed by esterification with methoxyacetyl chloride, provides ester **5** which undergoes an ester enolate Claisen rearrangement to provide acid **6** (Scheme **2**).[10,11] Conversion of this acid to phenyl ketone **7**, followed by reduction of the carbonyl functionality, provides the alkene **8** in 65% yield over 5 steps.[12] Ozonolytic cleavage of **8** to the respective aldehyde followed a Wittig reaction with isopropylidene triphenylphosphorane, produces the new trisubstituted olefin **9**. This compound is oxidized

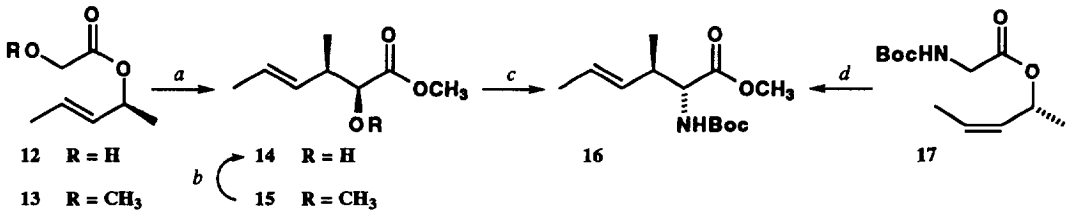
regioselectively by selenium dioxide to give the (*E*)- allylic alcohol (**10**). Some over-oxidation to the aldehyde occurs in this step, requiring treatment of the crude product with sodium borohydride to produce pure alcohol in 78% yield. This two step sequence conveniently avoids the formation of double bond isomers observed by earlier workers.[6] Compound **10** is converted to the phosphonium salt **11** in two steps as reported previously.[6]



Scheme **2**. *a*. i. Resolution as described in reference 9. ii. Na, NH_3, Et_2O, 90%. *b*. methoxyacetyl chloride, pyridine, CH_2Cl_2, 83%. *c*. KHMDS, TMSCl, THF, 81%. *d*. i. $Ph_2P(O)Cl$, $CH_3NH(OCH_3)$, THF, 95%. ii. PhMgBr, THF, 85%. *e*. i. $NaBH_4$, MeOH, 97%. ii. PhOC(S)Cl, pyridine, CH_2Cl_2 90%. iii. AIBN, nBu_3SnH, Toluene, 90%. *f*. i. O_3, DMS, MeOH, 86%. ii. $Ph_3P{=}CH(CH_3)_2$, THF, 80%. *g*. i. SeO_2, EtOH, ii. $NaBH_4$, 78%. *h*. Reference 6.

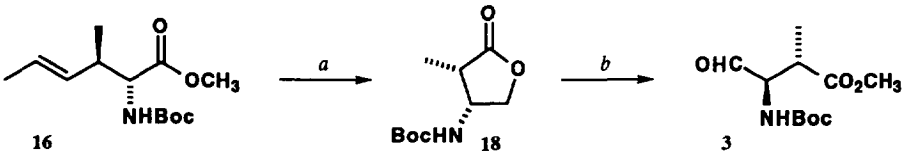
Several routes to fragment **3** have been explored. Claisen rearrangement of hydroxy ester **12**,[11] obtained from (*S*)-3-pentene-2-ol, followed by treatment with diazomethane provides the known methyl ester **14**.[10c] Alternatively, **14** may be obtained from the corresponding methyl ether (prepared as described above for the enantiomer), by demethylation using boron tribromide (Scheme **3**). Treatment of **14** with diphenylphosphoryl azide and DBU at room temperature gives no reaction.[13] However, under Mitsunobu conditions using diethyl azodicarboxylate the azide is obtained with clean inversion of configuration. Reduction of this azide to the amine and protection as its *tert*-butyl carbamate are performed in one pot to provide compound **16**.[14] Subsequently, it was found that compound **16** can be obtained directly from the glycine ester **17** using Kazmaier's modification of the Ireland-Claisen reaction.[15]

Reduction of ester **16** with lithium borohydride, followed by ozonolysis of the olefin in methanol provides lactone **18** (Scheme **4**).[16] Hydrolysis of this lactone, followed by esterification of the carboxylic acid and Swern oxidation of the primary alcohol, generates the required aldehyde **3** in 68% yield over three steps.[17]



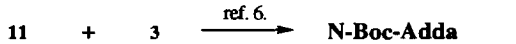
Scheme **3**. *a*. LHMDS, TMSCl, THF, 72% (R = H), 81% (R = CH_3). ii. CH_2N_2, Et_2O, quant. *b*. BBr_3, CH_2Cl_2, 65%. *c*. i. DEAD, Ph_3P, DPPA, THF. ii. Ph_3P, H_2O-THF. iii. $(Boc)_2O$, 60% over 3 steps. *d*. i. LDA, $ZnCl_2$, THF. ii. CH_2N_2, Et_2O, 72%.

Finally, fragments **3** and **11** are coupled using a Wittig reaction (Scheme **5**) and saponification of the methyl ester provides *N*-Boc-Adda in 48% over these two steps.[18]



Scheme **4**. *a*. i. $LiBH_4$, MeOH. ii. O_3, NaOH-MeOH, 63%. *b*. i. NaOH, MeOH-H_2O. ii. CH_2N_2, CH_2Cl_2. iii. DMSO, Et_3N, $(COCl)_2$, CH_2Cl_2, 68%.

In conclusion, *N*-Boc-Adda has been prepared in 15 steps and 9% overall yield from the readily available alcohol 3-pentyn-2-ol employing a route that includes two highly stereoselective ester enolate Claisen rearrangements.



Scheme **5**. Synthesis of *N*-Boc-Adda is completed with a Wittig reaction followed by saponification as described previously.[6]

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. Other abbreviations used in this manuscript: AIBN, azobis(isobutyronitrile); Boc-, *tert*-Butyloxycarbonyl-; $(Boc)_2O$, di-*tert*-butyl dicarbonate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethylazodicarboxylate; DMS, dimethyl sulfide, DMSO, dimethylsulfoxide; DPPA, diphenylphosphoryl azide; KHMDS, potassium bis(trimethylsilyl) amide; LDA, lithium diisopropylamide; THF, tetrahydrofuran; TMSCl, trimethylsilyl chloride.
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12. A derivative of compound **8**, prepared by ozonolysis followed by reduction to the alcohol, then acylation with (1*S*)-(-)-camphanic chloride, indicates that **8** is formed with >95% enantioselectivity.
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14. Examination of the mandelate ester prepared from compound **16** by saponification followed by condensation with methyl (*S*)-(+) mandelate indicates that **16** is formed with >95% enantioselectivity.
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17. The diastereomers of aldehyde **3** are separable by flash column chromatography.
18. Yields refer to chromatographically purified compounds showing spectroscopic data consistent with the assigned structures. Data for ***N*-Boc-Adda methyl ester** $[\alpha]_D^{25}$ = - 30.8° (c = 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (3H, d, *J* = 6.7 Hz), 1.22 (3H, d, *J* = 7.1 Hz), 1.45, (9H, s), 1.60 (3H, s), 2.54 - 2.82 (4H, m), 3.15 - 3.20 (1H, m), 3.23 (3H, s), 3.67 (3H, s), 4.36 (1H, br s), 5.28 (1H, br s), 5.37 - 5.46 (2H, m), 6.18 (1H, d, *J* = 15.6 Hz), 7.17 - 7.29 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8, 14.5, 16.3, 28.5, 36.7, 38.3, 44.1, 51.7, 54.6, 58.7, 79.4, 87.0, 125.3, 126.0, 128.2, 130.0, 132.5, 136.1, 136.3, 139.5, 155.6, 175.4; MS *m/z* $[M+H]^+$ calcd. 446.2906, found 446.2884.

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