Prayogik Rasayan

Synthetic studies of antascomicin A: Construction of C1-C16 fragment

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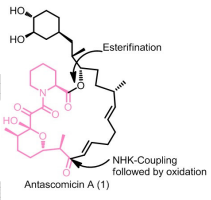
Abstract

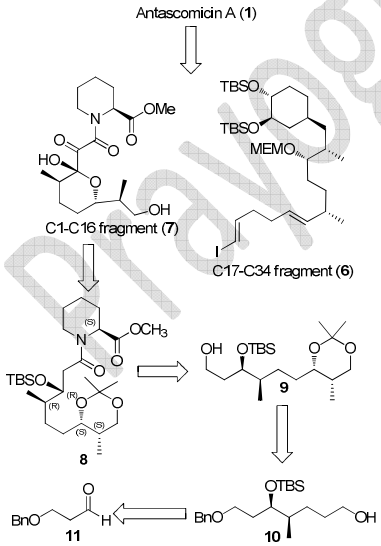
This communication describes the stereoselective synthesis of C1-C16 fragment of antascomicin A, a non-immunosuppressive immunophil-binding natural product. Evans aldol reaction was used extensively to install all the stereo centres present in the fragment. The hemikatel present in the fragment was synthesized via DMP-mediated oxidation of β-hydroxy amide followed by acid catalyzed hemiketalization.



Keywords: Immunosuppressive, FKBP12-binder, Anatscomicin A, Evans aldol and Lactamization.

Introduction

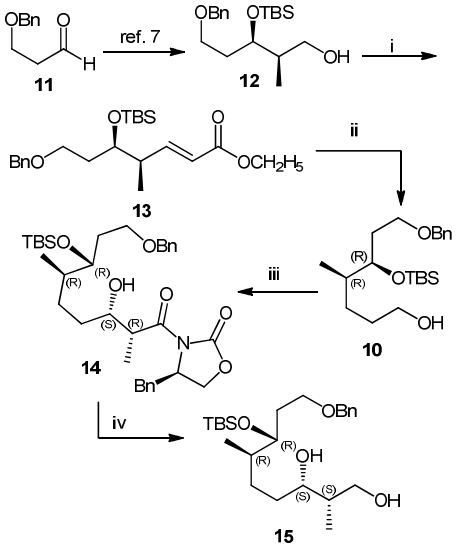
The antascomicins A-E are potent FKBP12-binding agent, which were isolated from fermenting a strain of the genus *Micromonospora* a soil sample collected in China.[1] Their ability to bind to FKBP12 is the same range as that of FK-506[2], cyclosporin A[3] and rapamycin.[4] FK-506 and rapamycin are potent inhibitors of T cell proliferation in the mixed lymphocyte reaction, whereas the antascomicns are inactive. There is no report on the total synthesis of antascomicin A till date, only one total synthesis of antascomicin B[5] and few synthetic studies of antascomicin A & B have been reported.[6] In this communication we report the synthesis of C1-C16 fragment of antascomicin A, where Evan's aldol reaction,[7] Horner-Wadsworth-Emmons reaction[8] and HATU mediated amide bond formation reactions[9] were used as key reactions.



Scheme 1: Retrosynthetic analysis

Results and Discussion

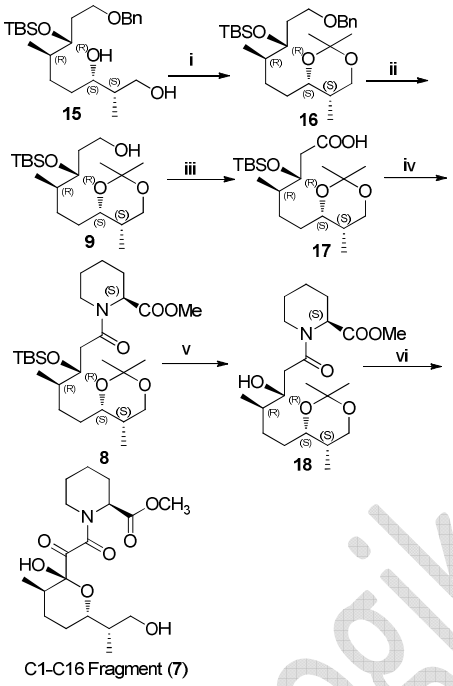
Inspection of the structure of antascomicin A, we realized that C1-C16 aldehyde of **7** and vinyl iodide **6** would be suitable precursors for the construction of the molecule via NHK-coupling reaction[10] followed by macrolactonization[11] (Scheme 1). The C1-C16 fragment **7** could be obtained from **8** via Dess–Martin periodinane oxidation[12] followed by acetonide deprotection under acidic conditions.[13] The ester **8** could be obtained from alcohol **9** via peptide coupling with (*S*)-methyl piperidine-2-carboxylate. The alcohol **9** might be obtained via Evans aldol reaction from **10**, which in turn would be obtained via Evans aldol reaction between from 3-benzyloxypropionaldehyde.



Scheme 2: Reagents and conditions for the synthesis of compound 15. (i) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ℃ to 0 ℃, 2 h; (b) $(EtO)_2POCH_2CO_2Et$, NaH, THF, 1h, 94% over two steps; (ii) $LiBH_4$, THF, 0 ℃ to rt, 2 h, 91%; (iii) (a)

$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ℃ to 0 ℃, 2 h; (b) (*R*)-4-benzyl-3-propionyloxazolidin-2-one, Bu_2BOTf, DIPEA, CH_2Cl_2, -78 ℃ to 0 ℃, 2 h, 80%; (iv) $NaBH_4$, THF:H_2O (10:1), 12 h, 88%.

The synthesis started from the known alcohol 12 (Scheme 2), which was prepared from well-known commercially available 3-benzyloxypropionaldehyde. The alcohol **12** was oxidized under Swern conditions,[14] to give an aldehyde, which under Horner-Wadsworth-Emmons reaction resulted α, β- unsaturated ester **13**. The α,β–unsaturated ester **13** was reduced to an alcohol **10** with $LiBH_4$,[15] which on oxidation followed by Evans aldol reaction gave secondary alcohol **14**. Reductive removal of chiral auxiliary gave the di-ol **15** in good yield.



Scheme 3: **Reagents and Conditions for the completion of the synthesis.** (i) 2,2 DMP, CSA, CH_2Cl_2, 1 h, 0 ℃, 93%; (ii) H_2, Pd/C, AcOEt, 2 h, 88%; (iii) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ℃ to 0 ℃, 2 h; (b) $NaClO_2$, NaH_2PO_4, ^tBuOH, 2-methyl-2-butene, 15 min; (iv) (*S*)-methyl piperidine-2-carboxylate, HATU, *N*-Ethyl piperidine, CH_3CN, 0 ℃, 73% over three steps; (v) CSA, 2,2- DMP:CH_2Cl_2(1:1), 0 ℃, 10 min, 86%; (vi) (a) DMP, Pyridine, CH_2Cl_2, 0 ℃, 3 h; (b) 1N HCl, 0 ℃, 30 min 80% over two steps.

The di-ol **15** was protected as its acetonide using 2,2-DMP and CSA (Scheme 3). The benzyl deprotection of **16** was carried out with H_2 in presence of Pd/C to give alcohol **5** in 88% yield.[16] The alcohol on oxidation followed by peptide coupling of the resulting acid with (*S*)-methyl piperidine-2-carboxylate in presence of HATU as coupling reagent gave compound **8**. TBS deprotection from compound **8** was carried out with CSA in 2,2-DMP and CH_2Cl_2 in 1:1 ratio to give secondary alcohol **18**. The active methylene group and secondary alcohol of **18** were oxidized with DMP[12] to give triketo intermediate that on acetonide deprotection followed in situ lactol formation under acidic conditions completed the synthesis of C1-C16 fragment **7** in 80% yield over two steps.

Conclusion

In conclusion, we have successfully achieved the synthesis of highly functionalized C1-C16 fragment of antascomicin A. The key feature of our synthesis includes Evan's aldol reaction, Horner-Wadsworth-Emmons reaction, Dess–Martin periodinane oxidation and HATU mediated amide bond formation reactions.

Acknowledgements

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