Facile synthesis of the acid-labile peptide amide linker containing the 10,11-dihydro-5H-dibenzo [a, d] cyclohepten-5-yl group

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Introduction
In a previous paper, linkers for peptide amide formation under mild conditions during Fmoc solid phase peptide synthesis were prepared based on the 10,11-dihydro-5H-dibenzo [a, d] cyclohepten-5-yl group (Sdibenzosuberyl group) and the 5H-dibenzo[a,d] cyclohepten-5-yl group (5-dibenzosuberenyl group) [1]. The more acid-sensitive linkers derived from these groups are cleaved in high yield at lower TFA concentrations. Many peptides have been made using these linkers with excellent yields and purities. However, the preparation of 2-(m-methoxyphenethyl) benzosic acid (4) needing catalytic hydrogenolysis of 3-(methoxybenzylidene)phthalide using Raney Ni (4 kg/cm², 50°C), was not suitable for large scale preparation. The present paper describes the facile synthesis of 3-methaxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one (5) prepared via m- methoxystilbene-2-carboxylic acid, and its conversion to the peptide amide linker of the 5-dibenzosuberyl group.

Results and discussion
The synthesis of m-methoxystilbene-2-carboxylic acid (3), the precursor of the key intermediate, 2-methoxy-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5-one (5), was reported by the Wittig reaction of the phosphonium salt derived from methyl 2-methylbenzoate with m-anisaldehyde [2]. The intermediate should be amenable to the more simple one-step synthesis for large scale preparation. The fusion reaction of 2-carboxybenzaldehyde and m-methoxyphenylacetic acid in the presence of sodium acetate gave rise to m-methoxystilbene-2-carboxylic acid with concomitant evolution of carbondioxide in 76% yield. The catalytic hydrogenation of 3 with 5% Pd-C gave 2-(methoxyphenethyl)benzoic acid (4), which was ringcylized by treatment of PPA to give 5 without any regioisomers in 86% yield. Demethylation of 5 with AlCl₃ afforded 6. The resulting OH group of 6 was alkylated with ethyl 5-bromovalerate in the presence of t-BuOK followed by hydrolysis of the resulting ester with aqueous NaOH to give corresponding acid 7. The reduction of 7 with NaBH₄
Figure 1. Synthesis of the peptide amide linker resins containing the 10,11-dihydro-5H-dibenzolo[a,d]cyclopenten-5-yl group. a: CH₃CO₂Na, 190°C; b: H₂ 5%Pd-C; c: PPA, 145°C; d: AlCl₃, benzene; e: t-BuOK, Br(CH₂)₄CO₂Et, DMF; f: NaOH, dioxane-H₂O; g: NaBH₄, isopropylalcohol; h: Fmoc-NH₂, pts, AcOH; i: TGS-NH₂, PyBOP-HOBT-IPEA, DMF.

gave the unstable alcohol (8). The easily formed alcohol cation in AcOH and a catalytic amount of p-toluenesulphonic acid (pts) was trapped with 9-fluorenylmethoxycarbamate (Fmoc-NH₂) to give the dibenzosuberyl linker (9) in 400% overall yield. The desired linker-resin range was achieved by coupling the polystyrene-polyethyleneglycol graft copolymer functionalized with the amino group (Tenta-Gel-S NH₂) using PyBOP-HOBT-DIPEA in DMF. The linker-resin analogue in which the dibenzosuberyl group was coupled to the resin with one carbon unit was prepared from 2-hydroxybenzosuberone (6) [2]. In order to assess the relative rate cleavage of 10 and 11, Fmoc Val derivatives prepared from 10 and 11 were treated with 50%TFA–5%phenol in DCM as a cleavage cocktail. Half lives of Fmoc Val were ca. 3 min for 10 and ca. 12 min for 11. The results indicated that the Fmoc Val derivative from 10 can be rapidly cleaved at a lower concentration of TFA than that from 11.