Efficient Solution and Solid-Phase Synthesis of a 3,9-Diazabicyclo[3.3.1]non-6-en-2-one Scaffold

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Abstract: The solution and solid-phase syntheses of a 3,9-diazabicyclo[3.3.1]non-6-en-2-one have been realised via sequential Dakin–West/Pictet–Spengler reactions.

Key words: bicyclic compounds, indoles, solid-phase synthesis, ring closure, cleavage

With the emergence of automated solution and solid-phase synthesis, combinatorial chemistry had become an essential tool in the discovery of new therapeutic agents. Since the first synthesis of peptide libraries, a large number of non-peptidic libraries have been produced, particularly heterocyclic libraries.[1] In the process of identifying new active scaffolds, one possible approach is to use the diversity pool of natural products as a guideline[2] to generate new templates. With this consideration in mind, our attention was attracted by the Saframycin, Safracin, Renieramycin and Ecteinascidin families (Figure), which show powerful antiproliferative and antitumoural properties thus making them very attractive targets.[3] In all these families, a common 3,9-diazabicyclo[3.3.1]non-6-ene core structure element was present. An indole 3,9-diazabicyclo[3.3.1]non-6-en-2-one structure has been selected as potential scaffold for combinatorial libraries. Here, we report the development of a highly efficient solution and solid-phase synthesis of this core structure. The synthesis of this type of structure has been already reported in the literature and the strategy was, in general, to produce first a β-carboline derivative between an aldehyde and tryptophan and then closing the bicycle or generating an acyl iminium for the cyclisation on an elaborated scaffold.[4] Our approach consists in a simple linear construction of the molecule before its cyclisation to the bicycle via an intramolecular Pictet–Spengler reaction. In addition, with our route, we are able to introduce a quaternary carbon with a define stereochemistry which enhances the potential diversity of our scaffold. A novel sequential Dakin–West/Pictet–Spengler reaction serves as key step of our synthetic route, which starts from L-tryptophan. Attachment of the template on solid-phase was achieved by using the commercially available L-5-hydroxy-tryptophan.

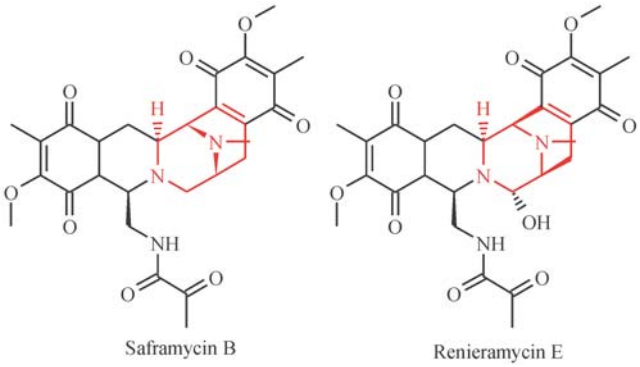

Figure Examples of structure from the Saframycin and Renieramycin families in red is outlined the core 3,9-diazabicyclo[3.3.1]nonene

Solution-Phase Synthesis

Dipeptide **2** was obtained in 63% yield after peptide bond formation between **1** and phenylalanine methylester and subsequent hydrolysis. Then, the carboxylic acid moiety was transformed to a methyl ketone unit through a Dakin–West[5] type reaction. Partial racemisation at the C-α stereocenter was observed under the required conditions. After hydrolysis, the methyl ketone derivative **3** as a mixture of 2 diastereoisomers (57/43) was obtained in 77% yield. Under acidic conditions (20% TFA in DCM), the Boc group was cleaved generating a free amino group, which immediately underwent intramolecular imine formation[6] with the methyl ketone. Then, an intramolecular Pictet–Spengler[7] cycli-sation reaction occurred yielding the 3,9-diazabicyclo[3.3.1]non-6-en-2-one derivative **4** (100% conversion, 62% isolated yield) (Scheme 1). The quaternary stereocenter generated during cyclisation is controlled through the asymmetric center of the L-tryptophan. Nevertheless, target structure **4** was obtained as a mixture of diastereoisomers (***cis*-4**/***trans*-4** 57/43) which were separated by flash chromatography on silica gel.[8] The *cis* or *trans* configuration (relative configuration between the methyl and the benzyl group) of the diastereoisomers was determined by modified ^{1}H-^{1}H ROESY experiments[9] on a BRUKER DPX 400 MHz. For the *cis* diastereoisomer, NOE effects were observed between (CH_2^{16})-NH^5 and CH_3^3-NH^5 whereas for the *trans* diastereoisomer, NOE effects were observed between (CH^{11})-NH^5 and CH_3^3-NH^5.

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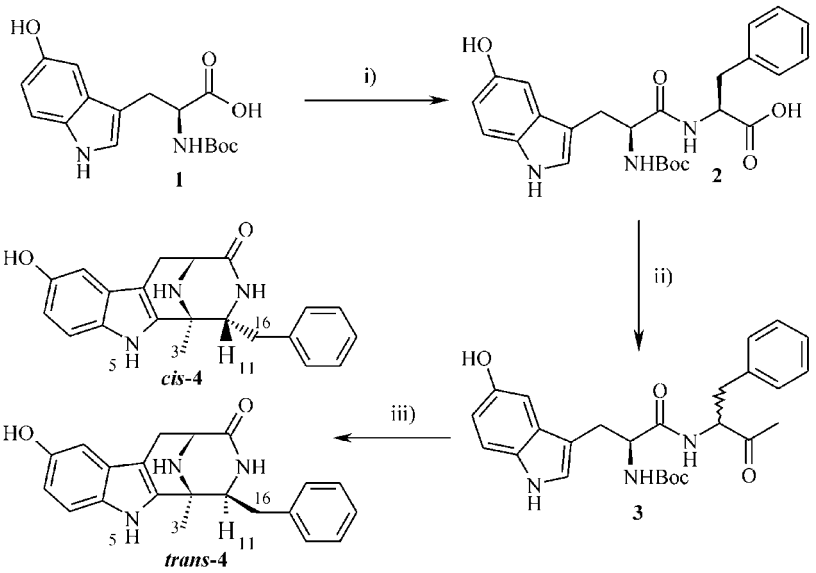
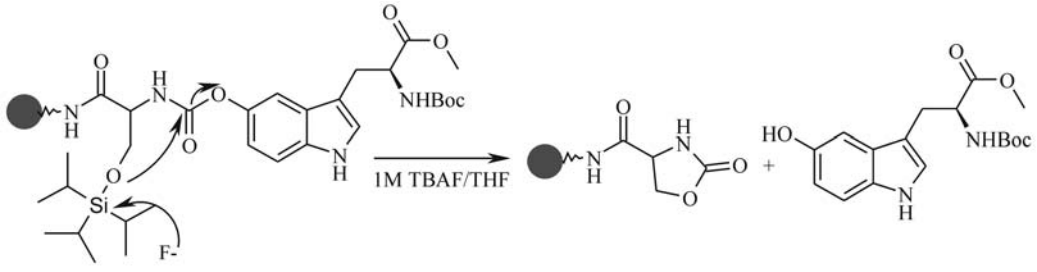


Scheme 1 Solution synthesis of 3,9-diazabicyclo[3.3.1]non-6-en-2-one scaffold. *Reagents and conditions*: i) a) HCl·H_2N-Phe-OMe, DCC, HOBt, Et_3N, THF, 16 h, r.t., b) NaOH 2N, THF, 2 h, r.t. (63%). ii) a) AcOH, Ac_2O, DMAP, Et_3N, THF, 16 h, 45 °C, b) NaOH 2N, THF, 2 h, r.t. (77%). iii) 20% TFA/CH_2Cl_2, 16 h, r.t. (62%).

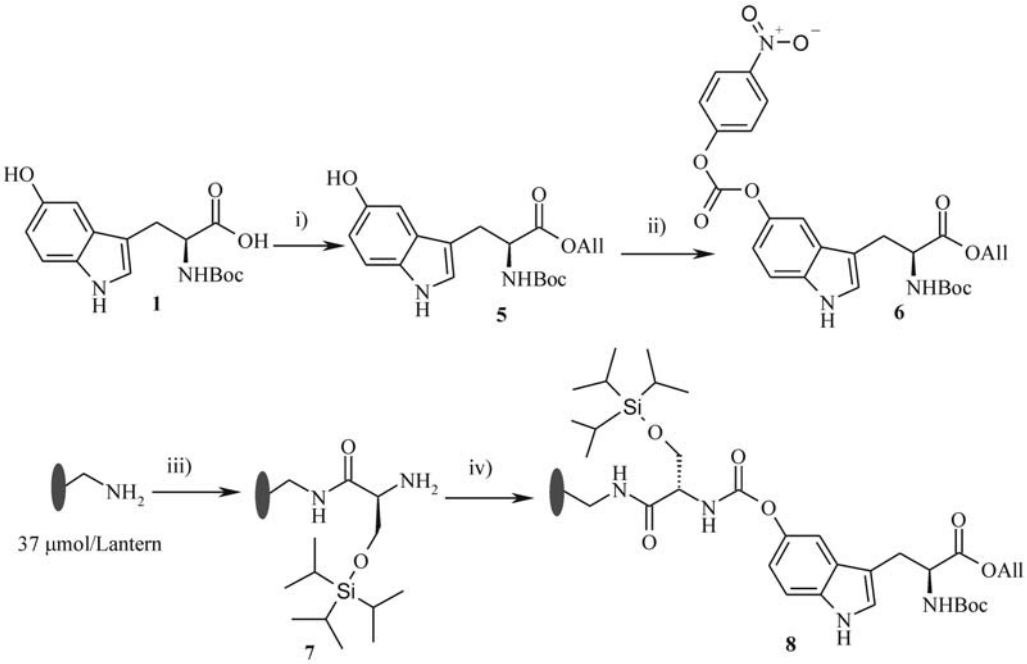
Mohan and co-workers reported a serine based carbamate linker for the attachment of phenolic compounds stable to TFA and organic bases.[10] The cleavage mechanism is based on the cleavage of the TIPS protecting group of a serine side chain with a 1 M TBAF/THF solution which provides an alkoxy ion able to attack intramolecularly the urethane linkage and so to release the phenol derivative. During his study, Mohan has used a BocNH-Trp(OH)-OMe template (Scheme 2).

Methylester hydrolysis of immobilised BocNH-Trp(OH)-OMe resulted in a significant product loss due to linker cleavage. No selective hydrolysis reaction conditions could be found. Therefore, we decided to replace the carboxylate-protecting group by an allyl ester function. We carried out a new efficient synthesis of the Mohan linker by using a preformed protected template prepared in solution before anchoring to the solid-phase. From **1**, esterification was performed under conditions described by Albericio and co-workers[11] with a mixture of allyl bromide and acetonitrile. After aqueous work-up, compound **5** was directly isolated by precipitation in hexanes in 63% yield and a purity greater than 95%. *p*-Nitrophenylcarbonate **6** was generated by treating **5** with paranitrophenyl chloroformate (66% yield after flash chromatography). Solid-phase experiments were performed on Synphase^{TM}.[12] The first part of the linker was introduced via peptide formation with BocNH-Ser(OTIPS)-OH. After Boc deprotection of the immobilised serine, template **6** was loaded on the solid-phase through the creation of an urethane bond (Scheme 3).

Solid-phase synthesis of the 3,9-diazabicyclo[3.3.1]non-6-en-2-one scaffold was initiated by removal[13] of the allyl group from functionalised resin **8**. Then, phenylalanine allyl ester was coupled under standard conditions and the allyl group was subsequently removed affording the free carboxylic acid **9**. Completion of the reaction was monitored by cleavage of cut off lantern's loops with 1 M TBAF/THF and analysis by LC/MS. The modified Dakin–West required significantly prolonged reaction times compared to its solution phase pendant to go to completion. Cyclisation with 20% TFA/CH_2Cl_2 at room temperature did not lead to any of the expected scaffold. Different conditions were examined resulting in complete cyclisation after 16 hours with 20% TFA in $C_2H_4Cl_2$ at 50 °C **(**Scheme 4).



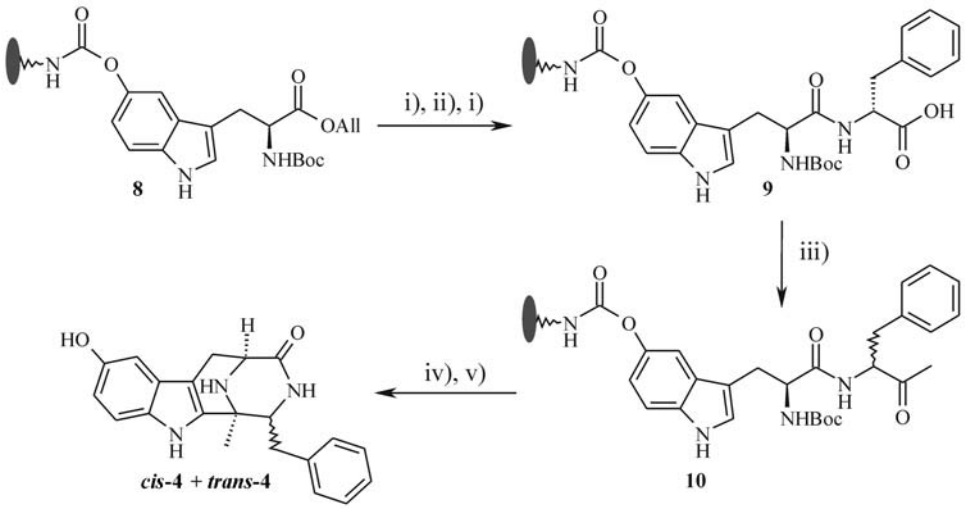
Scheme 2 Serine-based linker developed by Mohan



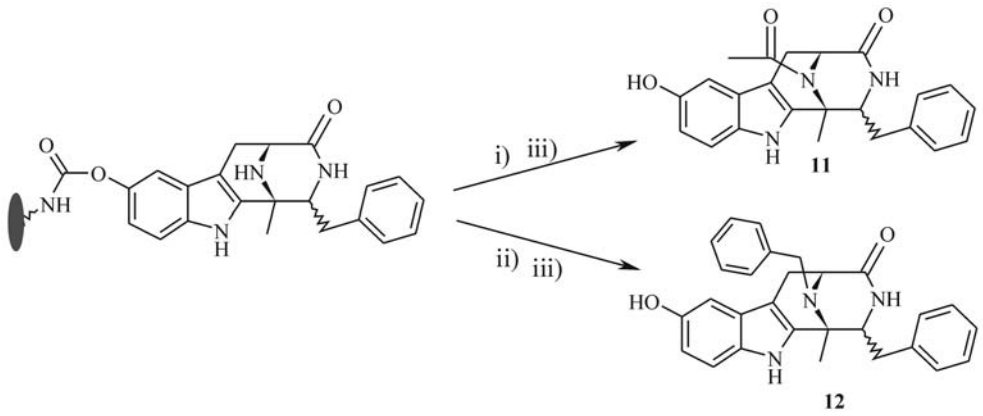
Scheme 3 Template synthesis and loading. *Reactions and conditions*: i) CH_3CN/allyl bromide (3/2, 10 mL per mmole of **1**), *i*-Pr_2EtN, r.t., 36 h (63%). ii) 4-$NO_2PhOCOCl$, Et_3N, Ch_2Cl_2, r.t., 5 h (64%). iii) a) BocNH-Ser(OTIPS)-OH, HOBt, DIC, NMM, THF, 50 °C, 24 h, b) 20% TFA/CH_2Cl_2, 2 x 90 min. iv) 6, TEA, CH_2Cl_2, 50 °C, 16 h.

Cleavage reactions with 1 M TBAF in THF solution were very efficient, however LC/MS analysis of the samples were sometimes tedious due to the presence of high concentrations of tetrabutylammonium salts, which saturated the mass detector. From our original experiments, we knew that cleavage was occurring when inorganic bases were used. Applying similar conditions, effective cleavage of the final scaffold was achieved with a cocktail solution containing NaOH (aq) 2 N/H_2O/THF (2/8/10) for 2 hours at room temperature. Target compound **4** was obtained in an overall yield of 35% (after 6 steps) with a purity of 85% by HPLC after aqueous work-up. The structure was confirmed by NMR and MS.

In addition, the immobilised scaffold was further functionalised. Acylation or alkylation on the bridged nitrogen was performed (Scheme 5). After cleavage, samples were analysed by LC/MS, which confirmed the mass of the expected materials with purities around 80% by HPLC for **11** and **12**.

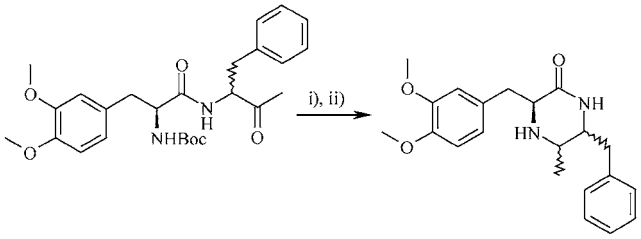


Scheme 4 Solid-phase synthesis of the 3,9-diazabicyclo[3.3.1]non-6-en-2-one scaffold. *Reagents and conditions*: i) Pd(II)acetate, PPh_3, morpholine, CH_2Cl_2, 2 h, r.t. ii) pTsOH·H_2N-Phe-OAll, Et_3N, DIC, HOBt, THF, 40 °C, 24 h. iii) Ac_2O, AcOH, DMAP, Et_3N, THF, 30 °C, 4 days. iv) 20% TFA/$C_2H_4Cl_2$, 50 °C, 16 h. v) 1M TBAF/THF, r.t., 2 h or NaOH 2N/H_2O/THF (2/8/10), r.t., 2 h.



Scheme 5 Functionalisation of the immobilised scaffold. *Reagents and conditions*: i) AcCl, Pyridine, CH_2Cl_2, 16 h, r.t. ii) BnBr, *i*-Pr_2NEt, DMF, 50 °C, 24 h. iii) NaOHaq 2N/H_2O/THF (2/8/10), r.t., 2 h.

In conclusion, we have shown an efficient solution and solid-phase synthesis of a novel diazabicyclo[3.3.1]nonenone core which might serve as an attractive scaffold for combinatorial libraries. The key step of this synthesis was a sequential Dakin–West/Pictet–Spengler reaction. Currently, optimisation of the linker and the cleavage conditions are under investigation as well as the diversification of the scaffold.



Scheme 6 i) 20% TFA/CH_2Cl_2, 16 h, r.t.; ii) $NaBH_4$, MeOH

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(8) For the *trans* diastereoisomer ^{1}H NMR (400 MHz, [d_6]DMSO, 26 °C): δ = 1.56 (s, 3 H, CH_3), 2.07 (dd, ^2J (H,H) = 13.97 Hz, ^3J (H,H) = 13.98 Hz, 1 H, C*H*HPh), 2.70 (d, ^2J (H,H) = 15.58 Hz, 1 H, IndC*H*H-), 2.88 (dd, ^2J (H,H) = 15.58 Hz, ^3J (H,H) = 6.44 Hz, 1 H, IndCH*H*-), 3.27 (dd, ^2J (H,H) = 13.97 Hz, ^3J (H,H) = 2.15 Hz, 1 H, CH*H*Ph), 3.72–3.78 (m, 2 H, C*H*NH and CC*H*NHCO), 5.93 (m, 1 H, N*H*CO), 6.60 (dd, ^3J (H,H) = 8.60 Hz, ^4J (H,H) = 2.15 Hz, 1 H, Ar*H*), 6.71 (d, ^4J (H,H) = 2.15 Hz, 1 H, Ar*H*), 7.16 (d, ^3J (H,H) = 8.60 Hz, 1 H, Ar*H*), 7.25 (t, ^3J (H,H) = 6.98 Hz, 1 H, *PhH*), 7.28 (d, ^3J (H,H) = 6.98 Hz, 2 H, Ph*H*), 7.34 (t, ^3J (H,H) = 6.98 Hz, 2 H, Ph*H*), 8.61 (s, 1 H, O*H*), 10.67 (s, 1 H, Indole N*H*). MS (negative electrospray): *m/z* (%) = 346 (100) [M – H]$^-$.
For the *cis* diastereoisomer ^{1}H NMR (400 MHz, [d_6]DMSO, 26 °C): δ = 1.44 (s, 3 H, CH_3), 2.67 (d, ^2J (H,H) = 15.04 Hz, 1 H, IndC*H*H-), 2.84 (dd, ^2J (H,H) = 15.04 Hz, ^3J (H,H) = 4.30 Hz, 1 H, IndCH*H*-), 2.95 (dd, ^2J (H,H) = 13.97 Hz, ^3J (H,H) = 13.97 Hz, 1 H, C*H*HPh), 3.12 (dd, ^2J (H,H) = 13.97 Hz, ^3J (H,H) = 4.83 Hz, 1 H, CH*H*Ph), 3.58 (m, 1 H, CC*H*NHCO), 3.73 (m, 1 H, C*H*NH), 6.97 (m, 1 H, N*H*CO), 6.55 (dd, ^3J (H,H) = 8.60 Hz, ^4J (H,H) = 2.14 Hz, 1 H, Ar*H*), 6.66 (d, ^4J (H,H) = 2.14 Hz, 1 H, Ar*H*), 7.08 (d, ^3J (H,H) = 8.60 Hz, 1 H, Ar*H*), 7.22 (t, ^3J (H,H) = 7.52 Hz, 1 H, *PhH*), 7.24 (d, ^3J (H,H) = 7.52 Hz, 2 H, Ph*H*), 7.32 (t, ^3J (H,H) = 7.52 Hz, 2 H, Ph*H*), 8.55 (s, 1 H, O*H*), 10.55 (s, 1 H, Indole N*H*). MS (negative electrospray): *m/z* (%) = 346 (100) [M – H]$^-$, 460 (25) [M + CF_3COO^-], 693 (5) [2 M – H]$^-$.
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