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# Design of an organic sequence suitable for the solid phase combinatorial synthesis of libraries of macro-heterocycles

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**Abstract**

The solid as well as solution phase synthesis of two 14-membered macro-heterocycles is reported. The macrocycles are built out of four or three major building blocks and contain serine, a *trans* alkene and the malonate unit inside the framework. The macrocyclization was an SN2 reaction between a nucleophilic malonate anion and an allylic chloride leaving group. The first macrocycle, an ether, was obtained with an overall yield of 8% for the eleven steps on solid support similar to the 11% yield in solution. The overall yield for the second target macrolactone was 45% on solid phase for the six steps and was higher than in solution (35%). The stability of the DHP linker to various reagents and reactions conditions is noteworthy.


*Introduction*. Whilst searching for an efficient way to build macrocycles from several building blocks on solid support, we have been studying tyrosine as a first building block.[1] According to the chemistry sequences developed then, the trifunctionalized amino acid tyrosine was attached to the resin through its acid part. However, in the name of molecular diversity it is desirable to use other groups as well for that purpose. In this paper we wish to report a new strategy where the first building block is attached to the resin by means of an alcohol. Such stratagem allowed us to carry out new chemistry to increase the bank of reactions compatible with the construction of large scaffolds on solid support. Ultimately this knowledge could then be used to design a new sequence of reactions amenable to automation and that could deliver, in a swift manner, a combinatorial library of biologically interesting macrocycles.[2] This paper relates this effort which finally provides us with a very efficient six-step synthetic scheme leading to macrolactones.

*Use of serine and DHP resin*. Serine like tyrosine is a tripod synthon which is usually linked to the resin through its acid end during SPPS (solid phase peptide synthesis). This means that final

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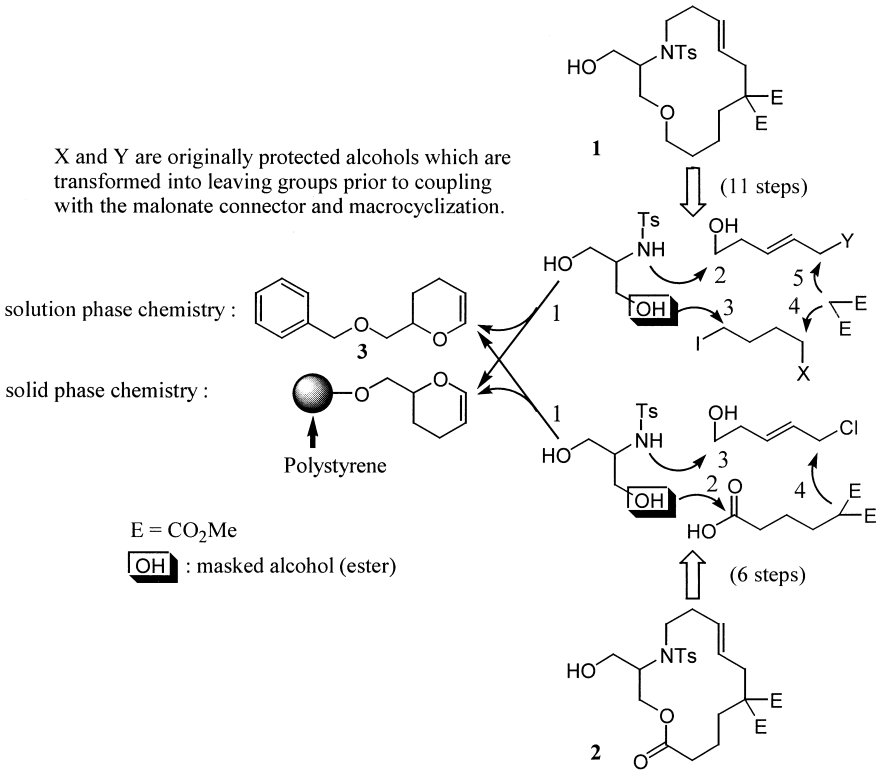
compounds, like macrocycles,[1] incorporating these α-amino acids used in a conventional manner would always bear acid pendant groups or their corresponding esters. Nevertheless, such amino acids possess two extra groups that could be used as a linkage to the resin; in particular serine can also be attached to the resin by its amine or its alcohol. Since the technology related to the alcohol is already known,[3] it was decided to explore that direction. Thus, following Ellman's procedure,[4] the DHP linker was attached to the Merrifield resin and serine could be coupled to the resulting DHP resin via its alcohol. The acetal which in fact corresponds to a THP ether should withstand a wide range of conditions including strong bases. Two targets have been studied in a sequential manner: The first target **1** is a 14-membered cyclic ether that required eleven steps to assemble it on solid support out of four building blocks (Scheme 1), whereas the second target **2** is an isosteric 14-membered lactone for which only six steps were necessary for its synthesis, because it was made from three instead of four building blocks.

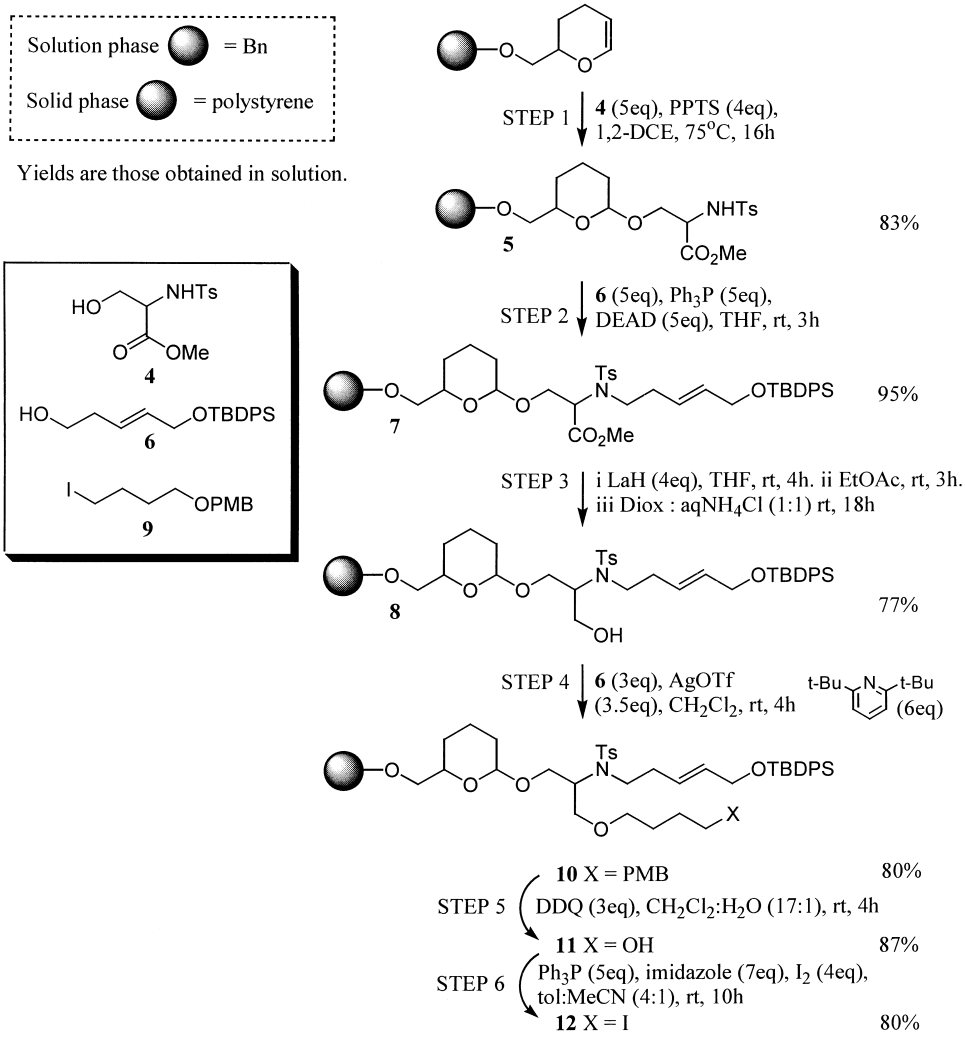



Scheme 1.

*Design and synthesis of the first target*. The first target is a 14-membered ring bearing one insaturation. Its construction requires eleven consecutive steps of SPOC (solid phase organic synthesis) amongst which five are coupling reactions; the remaining six steps being either deprotection, cleavage or functionnal group interconversion. Thus, the first coupling consists in the attachment of suitably protected serine to the DHP resin. Two chains are then sequentially added to the two remaining groups of serine to yield a fully alkylated serinol derivative. The last two coupling reactions allow the introduction of the last malonate connector and the macrocyclization of its corresponding anion by SN2 attack on the allylic chloride moiety. This sequence based on

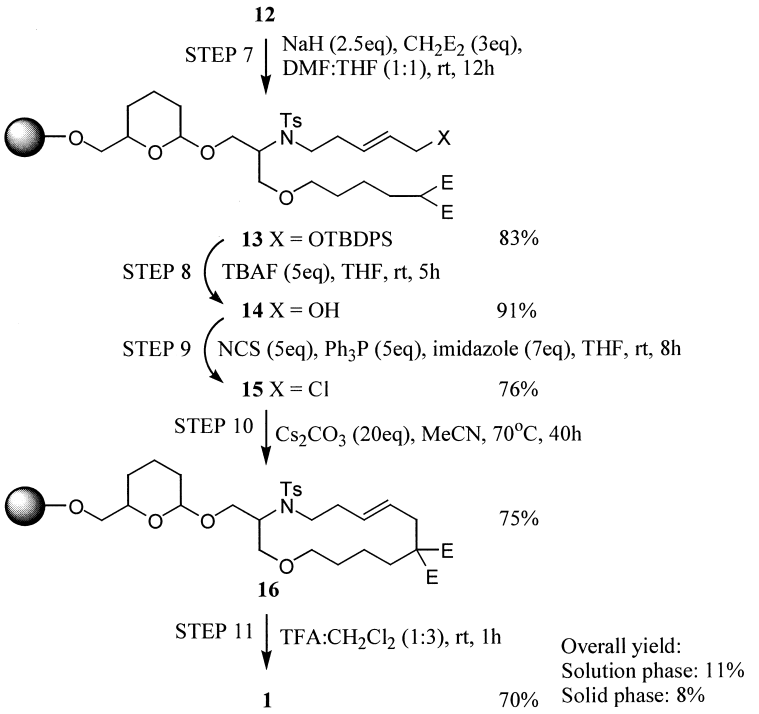
the DHP resin rendered possible the reduction of serine methyl ester to serinol by means of lithium aluminium hydride. Finally, in order to find the right conditions on the DHP resin, all the reactions were carried out in solution first with benzyl DHP resin model **3**.

The protected serine **4**[5] was coupled to the DHP resin by means of PPTS in 1,2-dichloroethane (yield of 83% for the same reaction in solution using benzyl DHP resin model **3**) (Scheme 2). The resulting tosylate **5** was subjected to Mitsunobu coupling conditions with the alcohol **6**[1] to obtain the ether **7** with an excellent yield of 95% (yield in solution). Then, lithium aluminum hydride reduction of the ester group afforded the serinol derivative **8** (77% yield in solution)[6]. A long (18 h) saturated aqueous ammonium chloride treatment had to be carried out to secure thorough removal of metal hydroxides. The alcohol **8** underwent ether formation with the iodide **9**[7] using silver triflate (despite the fact that silver nitrate was giving good results as well in solution; it proved not successful on solid support because it is less soluble than the triflate[8]). Under such conditions **10** was formed with a good yield of 80% (solution phase). Steps 5 and 6 consisted in




Scheme 2.

the cleavage of the PMB ether followed by activation of the resulting alcohol **11** to give the iodide **12**. Noteworthy, the DDQ reaction conditions[9] did not lead to resin-product cleavage at all; rather the reaction was entirely selective and high-yielded (87% in solution). The malonate connector was added (step 7) with a yield of 83% (solution) (Scheme 3). The remaining silyl protecting group was removed at step 8 by means of TBAF (91% in solution); the alcohol **14** was transformed into the corresponding allylic chloride **15** using NCS, triphenylphosphine and imidazole in a yield of 76% for the same reaction in solution. Finally the macrocyclization (step 10) went very well at 70°C by simply adding $Cs_2CO_3$ in acetonitrile to the allylic chloride precursor **15** and with a yield of 75% for the reaction in solution. This result confirms that the SN2 mode of cyclization is very powerful and that 14-membered rings bearing only one double bond are strain-free and consequently cyclize readily.[10] Treatment of **16** (solution model and solid phase) with TFA provided the same macrocycle **1**.[11]



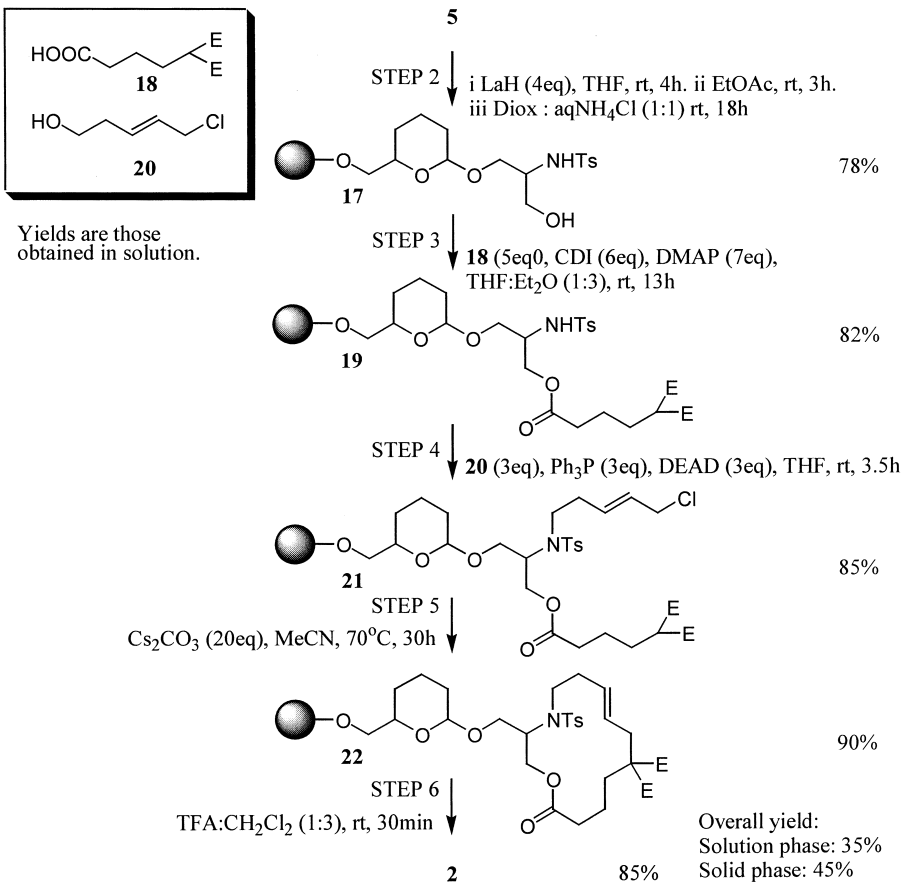

Scheme 3.

The overall yield of 8% for the SPOC synthesis of target **1** was evaluated according to the loading of the original Merrifield resin and compares well with the solution phase overall yield of 11%. We can therefore safely consider that all the yields observed for the solution phase individual steps were virtually identical to those obtained on solid support for the equivalent reactions. This indicates that all the reactions discussed here are perfectly suitable for SPOC and combinatorial chemistry.

*Design and synthesis of the second target*. In order to build libraries of macrocycles short sequences of SPOC should be envisaged for reasons of overall yields, purity and ease of manipulation. The DHP resin approach that we describe in this work appears to be versatile in terms of diversity at the amino acid site because all amino acids with an alcohol or a phenol group can be used.

However, the sequence shown above on the DHP resin is 11-step long because it took a lot of effort to introduce the malonate unit. It is therefore possible to shorten it dramatically the same way the tyrosine series was already reduced from 11 to six steps[1] as shown in Scheme 1. Thus, in order to simplify the previous DHP series, the number of building blocks was reduced from four to three, and the ether formation from an alcohol and an iodide with silver triflate was replaced by a mild and more versatile carbodiimide coupling between an alcohol and an acid. In summary, the prototype sequence of our future library gives a 14-membered lactone and is carried out in six steps. The three building blocks, from which diversity will emerge, are assembled by means of four coupling reactions: a THP protection with the DHP resin,[4] a carbodiimide coupling to form an ester, a Mitsunobu coupling and the cyclization reaction.

In solution, the methyl ester **5** (see Schemes 2 and 4) was reduced by means of lithium aluminum hydride (78%). Then step 3 was a CDI coupling[12] between the resulting alcohol **17** and the acid **18**[13] with a yield of 82%. The following reaction allowed the introduction of the allylic chloride moiety and consisted in a Mitsunobu coupling between the tosylamide group of **19** and the alcohol **20**[1] (85%). Noteworthy, this reaction takes place at a later stage (step 4) than in the previous similar six-step sequence.[1] Clearly, this represents an improvement because the resulting allylic chloride **21** is used right away. No doubt this improvement influences the final yield in a




Scheme 4.

very positive way. Then the macrocyclization was performed in the usual manner by means of cesium carbonate in acetonitrile at 70°C and with a yield of 90%. Finally, the THP protection was removed by means of TFA to give the final macrocycle **2**[14] (85%). The same procedure was then repeated on the DHP resin with a better overall yield.

The overall yield of 45% for the SPOC synthesis of macrocycle **2** (Scheme 4) was evaluated from the original loading of the Merrifield resin used to prepare the DHP resin. This yield is 10% higher than that obtained for the equivalent six-step sequence of reactions carried out in solution; it corresponds to the very high average yield of 88%.

*Conclusion*. This episode in the investigation of SPOC technology, ultimately destined to the creation of a library of macrocycles, led us to the establishment of a very efficient protocol suitable for combinatorial chemistry. Whilst keeping the complexity of the two target molecules **1** and **2** to the same degree during this work, it was finally possible to reduce the length of the sequence from 11 steps to merely six steps. The synthetic schemes take advantage of the DHP resin which allows us to carry out reductive reactions safely; the coupling reactions comprehend the very mild diimide and Mitsunobu conditions, resulting in the formation of *N*-alkylated and *O*-acylated serinol derivatives. Then, the macrocyclization occurs by means of SN2 attack of a malonate anion on an allylic chloride leaving group. Due to the very high overall yield obtained on solid support for macrocycle **2**, the prospect is very high and work is currently being pursued to actually build a large library of distinct macro-heterocycles. The three blocks **4**, **18** and **20** used in the model series can be swapped for other related synthons in a very straightforward way, hence the possibility of generating large and diverse libraries.

## Acknowledgements

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7. 1,4-Butanediol was monoprotected with PMB-Cl and DMF in THF (52%). The remaining alcohol group was transformed into the corresponding iodide with $Ph_3P$, MeI and DEAD to give **9** (84%).
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11. Macrocycle **1** analytical data: $^1$H NMR $\delta$ ($CDCl_3$): 1.2–1.65 (6H, m, 3 C$H_2$); 2.3–2.45 (4H, m, C$H_2$-CH=CH-C$H_2$); 2.49 (3H, s, C$H_3$-Ph-$SO_2$); 3.14 (2H, t, J = 4.5 Hz, C$H_2$N); 3.4–3.5 (4H, m, C$H_2$OC$H_2$); 3.68 (2H, d, J = 4 Hz, C$H_2$OH); 3.70 (3H, s, OC$H_3$); 3.74 (3H, s, OC$H_3$); 4.02 (1H, m, C*H*N); 5.3–5.5 (2H, m, C*H*=C*H*); 7.3–7.65 (4H,

m, *Ph*). $^{13}$C NMR $\delta$ ($CDCl_3$): 18.75, 20.82, 29.43, 31.36, 34.08, 34.90, 44.86, 52.10, 52.66, 59.38, 60.97, 62.84, 125.87, 127.16, 129.80, 132.19, 135.46, 143.56, 171.48, 171.66. IR $n$ ($cm^{-1}$): 3500br (OH); 1733 (C=O). HRMS: calcd $[M+H]^+$: 498.1349; found: 498.1358.

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13. The acid **18** was obtained by Jone's oxidation of the corresponding alcohol (62%) (see Ref. 1).
14. Macrocycle **2** analytical data: $^1$H NMR $\delta$ ($CDCl_3$): 1.4–1.8 (4H, m, 2 C$H_2$); 2.2–2.4 (4H, m, C$H_2$-CH=CH-C$H_2$); 2.43 (3H, s, C$H_3$-Ph-$SO_2$); 2.60 (2H, t, J = 6.5 Hz, -C$H_2$-CO); 3.21 (2H, m, C$H_2$N); 3.4–3.6 (4H, m, HO-C$H_2$-CH-C$H_2$O); 3.71 (3H, s, OC$H_3$); 3.73 (3H, s, OC$H_3$); 3.97 (1H, tt, J = 6 and 6.5 Hz, C*H*N); 5.15 (1H, m, C*H*=CH); 5.45 (1H, m, C*H*=CH); 7.25–7.35 (2H, m, *Ph*); 7.65–7.75 (2H, m, *Ph*). $^{13}$C NMR $\delta$ ($CDCl_3$): 19.10, 21.52, 30.82, 32.38, 34.27, 34.92, 45.02, 52.57, 52.66, 59.26, 60.80, 62.81, 125.87, 127.39, 129.75, 132.38, 137.48, 143.57, 171.48, 171.64, 172.81. IR $n$ ($cm^{-1}$): 3300br (OH); 1733 (C=O). HRMS: calcd $[M+H]^+$: 512.1954; found 512.1958.