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Solid-phase synthesis of hydroxy-acids leading to macrolactones

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Abstract

A sequence of five chemical steps on solid support yields hydroxy-acids in a very straightforward and efficient manner. The resulting compounds can be cyclized in solution phase by forming an ester bond to produce macrolactones. © 2000 Published by Elsevier Science Ltd.

Introduction. In our previous efforts[1] to develop a powerful methodology to build libraries of macrocycles on solid support, the crucial macrocyclization step was carried out on solid support and by forming a carbon–carbon bond. However, since original results indicated that the high dilution conditions usually necessary to macrocyclize could not be met on solid support,[2] then a parallel research project was started to solve that problem. The alternative route consists in preparing the cyclization precursors on solid support and then cyclizing them in solution; the description of this particular work is the topic of this letter.

Design of the sequence. Macrolactones were chosen as targets for this project because they have potential biological activity as shown by many members of the macrolide family,[3] It was decided to macrocyclize by forming an ester bond instead of a carbon–carbon bond as was usually done in all our previous work.[1,4] Since the macrolactonization was to be carried out in solution, it ensues that hydroxy-acids had to be prepared on solid support and in as little chemical steps as possible. To be able to accomplish this, it was necessary to reduce the number of functional group deprotection steps to the minimum. In fact, beside the cleavage of the resin (which, to some extend can be considered as functional group deprotection) there remained only one such step. The formation of an hydroxy-acid requires five steps on solid support as summarized in Scheme 1.

The first step is the hooking of the first building block to the Wang resin by esterification. Then the second building block is directly attached to the growing chain by SN2 displacement of a

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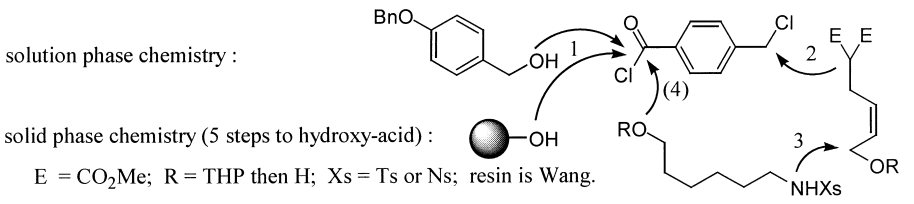
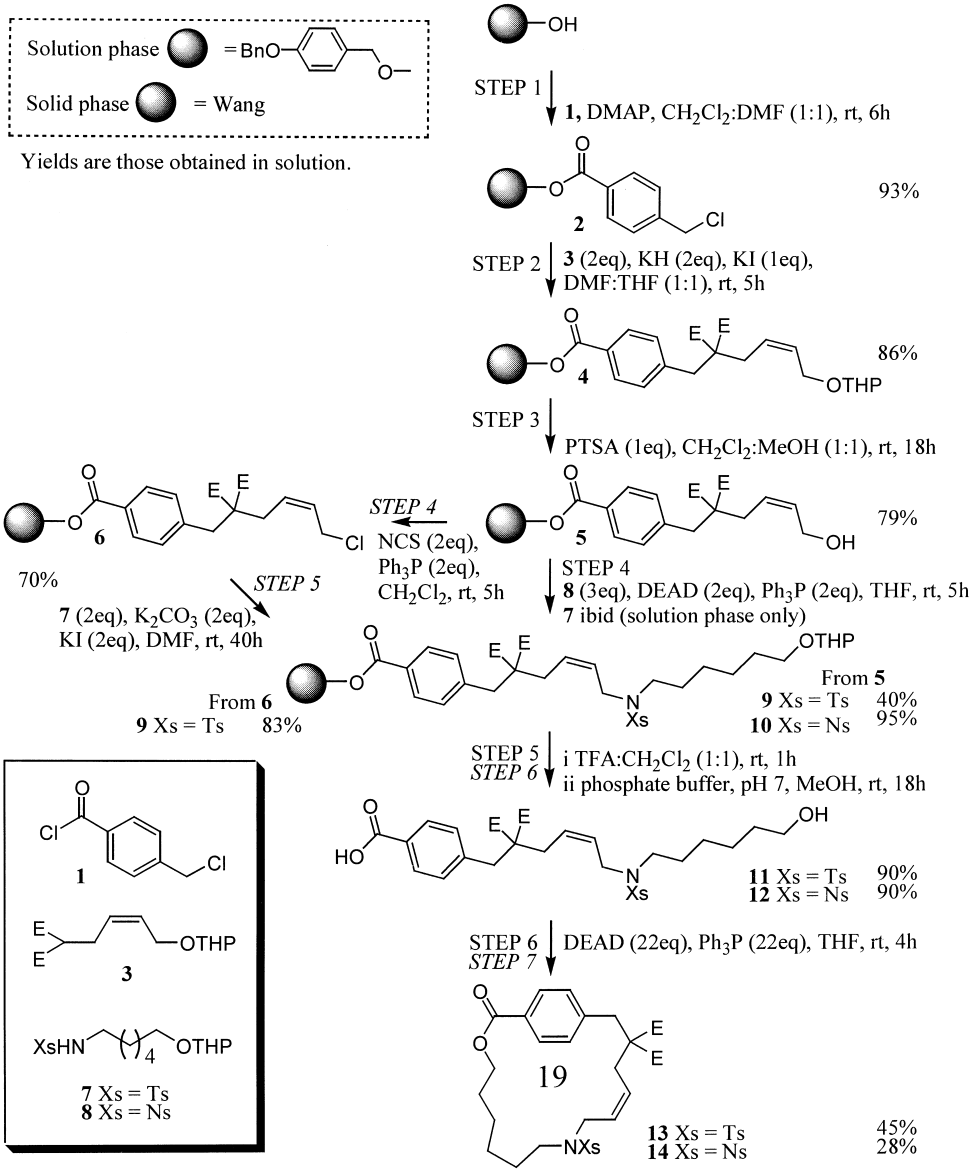


Scheme 1.

benzylic chloride by means of a malonate anion.[5] An alcohol is then set free and coupled to the last building block by Mitsunobu coupling.[6] This leaves only the cleavage of the hydroxy-acid off the resin and eventually the lactonization of the resulting compound in solution. The chemistry was fine-tuned in solution using 4-benzyloxy benzyl alcohol as a resin model, and the best conditions found were adapted to solid-phase chemistry to produce two lactones **13** and **14** (Scheme 2).

Chemistry. For the solution-phase chemistry the Wang resin was replaced by *p*-benzyloxy benzyl alcohol. The first step consisted of the esterification of that alcohol with the acid chloride **1**, the first building block, and with a yield of 93%. The resulting benzyl chloride in **2** was treated with the anion of the malonate **3**,[5] the second building block. The SN2 displacement reaction produced the desired THP ether **4** with a yield of 86%. The THP ether was then cleaved at step 3 with PTSA (yield: 79%) to produce the corresponding alcohol **5** necessary for the subsequent Mitsunobu coupling. Thus, at step 4, the tosylamide **7**[7] was added to the allylic alcohol **5** as well as DEAD and triphenylphosphine. However, the desired compound **9** was only obtained with the very disappointing yield of 40%. Because of this low yield, this reaction was never tried on solid support. In order to get **9** with better results and to find a safer route for solid-phase chemistry, the allylic alcohol **5** was transformed into the allylic chloride **6** by means of *N*-chlorosuccinimide and triphenylphosphine (yield: 70%). The allylic chlorine atom of **6** was then displaced in an SN2 fashion by the anion of the tosylamide **7** and with a good yield of 83%. Even in this alternative route, the swiftness sought for was lost because the sequence was then one step longer than originally planned. Consequently, the only parameter which was left for possible modifications is the nature of the sulfonamide Xs on compound **7**; the acidity of the NH proton was increased by replacing the tosyl group by a nosyl (*o*-nitrobenzene sulfonyl) group.[8] The resulting nosylamide **8**[7] underwent Mitsunobu coupling with the alcohol **5** to produce **10** with the excellent yield of 95%. It was therefore unnecessary in the case of **8** to investigate the alternative route via the allylic chloride **6**. The next step allowed deprotection of both the alcohol and the carboxylic acid functionalities. The benzyloxy benzyl ester group hydrolysis in solution was equivalent to the cleavage from the Wang resin. Trifluoroacetic acid was used for that double purpose. The desired hydroxy-acids **11**[9] and **12**[10] were obtained together with various amounts of the corresponding trifluoroacetates; hence the subsequent treatment of the reaction mixtures with methanol under neutral buffered conditions to get them as pure compounds with yields of 90% in both cases. The two hydroxy-acids **11** and **12** were then treated with DEAD and triphenylphosphine to provoke their lactonization. The 19-membered lactones **13**[11] and **14**[12] were obtained with the respective yields of 45 and 28% under these conditions. Thus, the hydroxy-acid **11** was obtained in five steps (Mitsunobu route) with an overall yield of 23%, while the alternative six-step route (SN_2 via allylic chloride **6**) yielded the same compound **11** with a better overall yield of 33%. On the other hand, the other five-step route leading to **12** was much more successful since the overall yield was 54%.



Scheme 2.

The same sequences, six steps in the case of **11** and five steps for **12**, were carried out on solid support using the same conditions. The overall yields were 23 and 50% after flash chromatography of the crudes. Therefore, the solid-phase routes were lower yielded than the solution-phase routes by as much as 10% in the case of **11**. The overall yield were evaluated from the original loading of the Wang resin.

Conclusion. The chemistry described here is very efficient at producing hydroxy-acids. The method seems rather robust so that it should be general and could also be applied to more elaborate hydroxy-acids and even to amino acids by varying the nature of the third building block. However,

the tosylamide group is not as good at coupling with alcohols under Mitsunobu conditions as previously observed.[1] In the current case the tosylamide is prepared from an isolated primary amine; whereas in the past projects the tosylamides were always originating from α-amino-acids. In that particular case, the α-carbonyl should obviously pull the electrons from the NH group and its proton should be more acidic, and consequently the Mitsunobu coupling should be eased. This positive effect cannot take place in the present work and the Mitsunobu coupling goes poorly with the tosylamide group. The nosylamide group solves the problem completely since the nitro group produces the same favorable electro-withdrawing effect to an even larger extent; it is therefore the best choice as a sulfonamide if a library of hydroxy-acids like **11** and **12** was to be prepared according to the chemistry shown. On the other hand the sequence may not be well suited for the preparation of arrays of lactones like **13** and **14** because the extra step in solution might be detrimental to efficient automation.

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7. 6-Aminohexan-1-ol was treated with TsCl and 2N NaOH in ethyl acetate and water to yield the corresponding tosylamide (85%) whose alcohol was protected as a THP ether (PTSA and DHP) to give **7** in 68% yield. Compound **8** was obtained in the same manner from 6-Aminohexan-1-ol and NsCl with a yield of 54% for the two reactions.
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9. Hydroxy-acid **11** analytical data: ^{1}H NMR δ ($CDCl_3$): 1.25 (4H, m, $CH_2CH_2CH_2CH_2N$), 1.49 (4H, m, $CH_2CH_2CH_2CH_2CH_2N$), 2.43 (3H, s, CH_3-Ph-SO_2), 2.46 (2H, d, J = 5 Hz, $CH_2CH{=}CHCH_2N$), 3.05 (2H, m, CH_2CH_2N), 3.29 (2H, s, CH_2ArCO_2), 3.60 (2H, t, J = 6 Hz, CH_2OH), 3.72 (8H, br s, $CH{=}CHCH_2N$ and OCH_3), 5.44 (2H, m, $CH{=}CH$), 7.11 (2H, d, J = 8 Hz, *Ar*), 7.28 (2H, d, J = 8 Hz, *Ar*), 7.65 (2H, d, J = 8 Hz, *Ar*), 7.98 (2H, d, J = 8 Hz, *Ar*). ^{13}C NMR δ ($CDCl_3$): 21.4, 25.1, 26.2, 28.2, 30.0, 32.3, 38.3, 44.7, 47.6, 52.7, 58.3, 62.5, 126.0, 127.0, 128.4, 129.2, 129.6, 129.9, 130.1, 136.8, 141.8, 143.2, 170.7. MS (CI, NH_3): 557 $[M–MeOH]^+$.
10. Hydroxy-acid **12** analytical data: ^{1}H NMR δ ($CDCl_3$): 1.27 (4H, m, $CH_2CH_2CH_2CH_2N$), 1.48 (4H, m, $CH_2CH_2CH_2CH_2CH_2N$), 2.51 (2H, d, J = 5 Hz, $CH_2CH{=}CHCH_2N$), 3.23 (2H, m, CH_2CH_2N), 3.32 (2H, s, CH_2ArCO_2), 3.61 (2H, t, J = 6 Hz, CH_2OH), 3.74 (6H, s, OCH_3), 3.87 (2H, d, J = 5 Hz, $CH{=}CHCH_2N$), 5.51 (2H, m, $CH{=}CH$), 7.15 (2H, d, J = 8 Hz, *Ar*), 7.6–7.7 (4H, d, *Ar*), 8.00 (2H, d, J = 8 Hz, *Ar*). ^{13}C NMR δ ($CDCl_3$): 25.2, 26.2, 27.9, 30.2, 32.3, 38.5, 44.1, 47.4, 52.7, 58.4, 62.6, 124.2, 127.0, 128.5, 128.8, 129.9, 130.3, 130.6, 130.8, 131.7, 133.5, 141.8, 147.9, 170.8. MS (EI, 70 eV): 603 $[M–OH]^+$.
11. Macrocycle **13** analytical data: ^{1}H NMR δ ($CDCl_3$): 1.40 (4H, m, $CH_2CH_2CH_2CH_2N$), 1.50 (2H, m, CH_2CH_2N), 1.74 (2H, m, CH_2CH_2O), 2.21 (2H, br s, $CH_2CH{=}CHCH_2N$), 2.41 (3H, s, CH_3–Ph–SO_2), 3.01 (2H, m, CH_2CH_2N), 3.25 (2H, br s, $CH{=}CHCH_2N$), 3.36 (2H, s, CH_2ArCO_2), 3.81 (6H, s, OCH_3), 4.40 (2H, m, CH_2O), 5.17 (2H, m, $CH{=}CH$), 7.07 (2H, d, J = 8 Hz, *Ar*), 7.25 (2H, d, J = 8 Hz, *Ar*), 7.62 (2H, d, J = 8 Hz, *Ar*), 7.88 (2H,

d, J = 8 Hz, *Ar*). ^{13}C NMR δ ($CDCl_3$): 21.5, 26.7, 28.0, 29.1, 29.5, 37.9, 46.0, 48.8, 53.0, 56.9, 66.3, 124.9, 127.1, 129.5, 129.8, 137.9, 140.9, 143.0, 165.8, 171.2. MS (EI, 70 eV): 571 $[M]^+$, 540 $[M–MeO]^+$. HRMS: calcd $[M]^+$: 571.2240; found: 571.2233.

12. Macrocycle **14** analytical data: ^{1}H NMR δ ($CDCl_3$): 1.3–1.55 (6H, m, $CH_2CH_2CH_2CH_2N$), 1.74 (2H, m, CH_2CH_2O), 2.19 (2H, br s, $CH_2CH{=}CHCH_2N$), 3.18 (2H, m, CH_2CH_2N), 3.36 (2H, br s, $CH{=}CHCH_2N$), 3.37 (2H, s, CH_2ArCO_2), 3.81 (6H, s, OCH_3), 4.42 (2H, t, J = 5 Hz, CH_2O), 5.19 (2H, m, $CH{=}CH$), 7.09 (2H, d, J = 8 Hz, *Ar*), 7.25 (2H, d, J = 8 Hz, *Ar*), 7.5–7.7 (2H, m, *Ar*), 7.92 (2H, d, J = 8 Hz, *Ar*). MS (EI, 70 eV): 602 $[M]^+$. HRMS: calcd $[M]^+$: 602.1934; found: 602.1939.