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Design and synthesis of macro-heterocycles structurally related to tirofiban

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Abstract

Sequences of nine and four steps were designed to yield two tirobifan related macrocycles by SN2 macrocyclization. The cyclic compounds contain the amino acid tyrosine, one insaturation and are either 18- or 20-membered rings. All the reaction conditions are very mild and the overall yields indicate that the results depend a lot on the structure of the targets and on the length of the reaction sequence. © 2000 Published by Elsevier Science Ltd.

1. Introduction

A class of organic structures with outstanding pharmaceutical activity has been termed the macrocycle family. Compounds like Epothilone,[1] Erythromycin, Neocarzinostatin, Rifampin and Amphotericin are under clinical study or already marketed drugs and belong to this important family. Although very diverse[2] in terms of chemical nature, the macrocycles share a very important property: restricted conformational mobility. Once bioactivity is found, the search for the active conformation is eased. With that important aspect in mind we became interested in the design and synthesis of specific macrocycles that could be used to find very useful conformational information on very flexible lead compounds or even marketed drugs. Some of our past research dealt precisely with the construction of macro-carbocycles[3] from various sets of building blocks. In principle this type of building block approach should be easily adapted to SPOC (solid phase organic chemistry) synthesis and potentially useful macrocyclic scaffolds could be obtained in a combinatorial fashion.

N-(*n*-Butanesulfonyl)-*O*-(4-(4-piperidinyl)-butyl)-(*S*)-tyrosine **1** (Scheme 1) is a potent glycoprotein (GP)IIb/IIIa blocker[4] also known as Tirofiban and marketed under the name Aggrastat.

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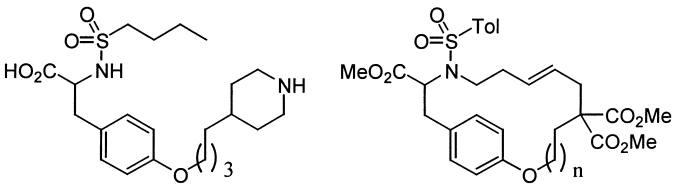
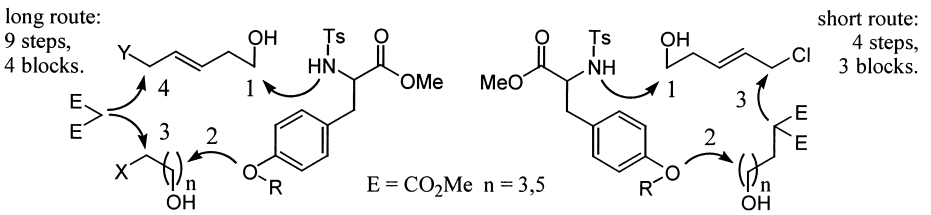
It is an anti-platelet aggregation agent used in various vascular pathologies. The construction of conformationally more rigid analogs of this very flexible molecule could permit the determination of the pharmacophoric conformation and eventually lead to even more potent lead compounds. This letter describes the synthesis of macro-heterocycles **2** and **3** built around the trifunctional α-amino tyrosine (Scheme 2) and that share many common features with Tirofiban **1**.



1 **2** n = 3 **3** n = 5

Scheme 1.

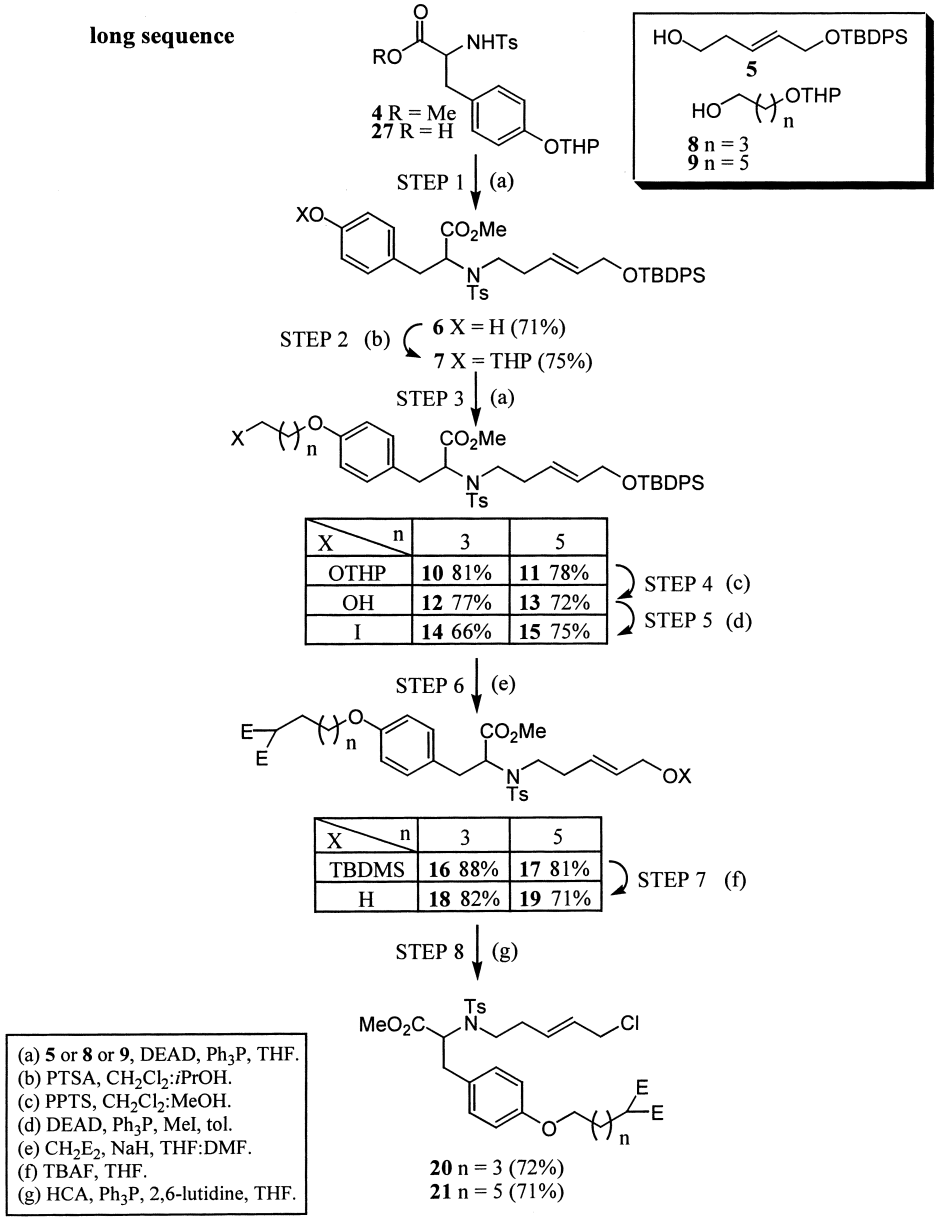


Scheme 2.

Use of tyrosine. The malonate unit was successfully used as a first connector in all our previous investigation series.[5] However, we looked for alternative first connectors that bear at least three functional groups. This could allow straightforward hooking to a resin (e.g. Wang), and sequential alkylation or acylation of the two remaining sites. Several amino acids fill that bill and have the advantage of being part of numerous natural ligands. For the present work, dealing with the synthesis of macrocycles related to Tirofiban, tyrosine was chosen and was protected in a suitable way (**4**)[6] (Scheme 3).

Solution chemistry. The two target macrocycles **2** and **3** were synthesized during this study. Mild *N*- and *O*-alkylation methodologies (Mitsunobu[7] couplings) were used to assemble the building units. The macrocycles were formed at a late stage by malonate anion reaction on allylic chlorides.[8] Macrocycles **2** and **3** were both prepared according to two sequences: a long sequence requiring nine steps and a short four step sequence as summarized in Scheme 2 and detailed in Schemes 3–5.

Long multistep synthesis. The protected tyrosine **4**[6] was subjected to Mitsunobu coupling with the alcohol **5**[8] to obtain **6** (75%) (Scheme 3). After the deprotection of the phenol with PTSA and methanol in dichloromethane (71%), **7** was subjected to another Mitsunobu reaction with both the diols **8**[9] and **9**;[10] the yields of **10** and **11** were again high (about 80%). After THP cleavage (step 4) (around 75%), the alcohols **12** and **13** were converted to the corresponding iodides **14** and **15** with DEAD, Ph_3P and MeI in toluene (66% and 75%). With these iodides in hand, the next



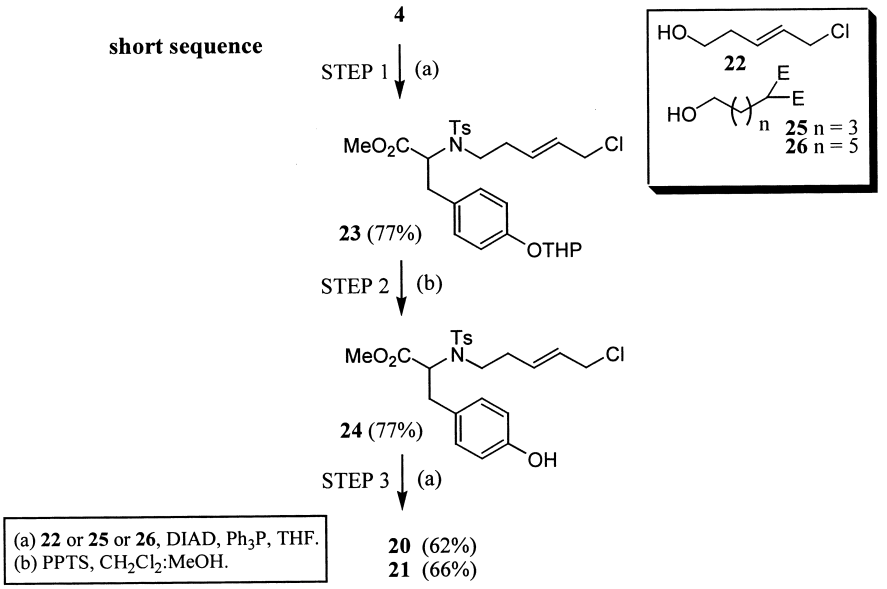
X \ n	3	5
OTHP	**10** 81%	**11** 78%
OH	**12** 77%	**13** 72%
I	**14** 66%	**15** 75%

X \ n	3	5
TBDMS	**16** 88%	**17** 81%
H	**18** 82%	**19** 71%

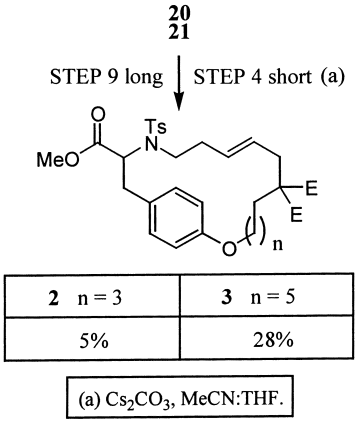
Scheme 3.

step 6 involved the formation of the malonates **16** and **17** under standard conditions[11] and in good yields (85%). After deprotection of the silyl group by means of TBAF (step 7) (82 and 71%), the resulting alcohols **18** and **19** were chlorinated by means of HCA and Ph_3P in good yields (around 70%) to give the precursors of cyclization **20** and **21**.

Short multistep synthesis. A new approach to build the two allylic chlorides **20** and **21** already synthesized was investigated with the optic of reducing the length of the sequence (i.e. three steps only, rather than eight) (Scheme 4). This was made possible by removing non-productive steps



Scheme 4.



Scheme 5.

like group deprotections and also by performing four instead of five connections. The latter modification was a consequence of the decrease in the number of building blocks (the new third building block being in fact a fusion of the third and fourth blocks used at first). Since recourse to anion chemistry was not necessary before the SN2 macrocyclization step, the allylic chloride functionality could be introduced at an earlier stage than before by means of the very mild Mitsunobu alkylation conditions. This usually highly reactive allylic chloride could then survive all subsequent reactions until the ring formation step due to the general mildness of the whole sequence. Thus, *trans*-1-chloro-2-penten-5-ol **22**[12] was coupled to the tosylate **4** under Mitsunobu conditions with DIAD and with a yield of 77% (step 1). Step 2 consisted in the cleavage of the THP ether by means of PTSA in a 1:1 mixture of dichloromethane and methanol (77%). The resulting phenol **24** was transformed into the same two cyclization precursors **20** and **21** as in the

first approach and by means of Mitsunobu couplings with the alcohols **25**[13] and **26**[14] (yields of 62 and 66%, respectively).

Macrocyclization. The macrocyclization (step 9 for the long sequence and step 4 for the short sequence) was carried out at 75°C by simply adding Cs_2CO_3 in acetonitrile and THF to the allylic chloride precursors **20** and **21** and produced the macrocycles **2** and **3** with yields of 5 and 28%. These low yields indicate that the SN2 transition structures leading to the macrocycles **2** and **3** are strained despite the presence of many insaturations. It can be observed that some tension is relieved when the macrocycle becomes larger since the 18-membered ring **2** is almost not present (the reaction mixture is very complex and **2** could only be detected by LC-MS) whereas the 20-membered ring compound **3**[15] is obtained in substantial amount.

Solid phase chemistry. The protected tyrosine **27**[6] (see Scheme 3) was coupled to the hydroxymethyl resin by means of DIC and DMAP in dichloromethane. All the solution phase chemistry described above (long and short sequences) was then repeated on solid support and the cleavage step was carried out by means of sodium methoxide. The long sequence yielded none of the expected products and **2** was not obtained either through the short sequence. On the other hand the 20-membered macrocycle **3** was formed with an overall yield of 5% with the short sequence protocole.

Conclusion. The aim of this work was twofold: Our primary goal was to develop a simple and versatile method to build macro-heterocycles useful to investigate the bioactive conformation of very flexible leads or drugs like Tirofiban. We were also interested in studying both the effect of the length of the reaction sequences and of the geometrical characteristics of the target macrocycles on the overall yields. Two macrocycles **2** and **3** of 18- and 20-members had been selected for this work. They proved to be difficult cases because only the larger less strained macrocycle **3** could be obtained in a very clean way both in solution and also on solid support. On the whole, the technology that we have developed to build macro-heterocycles of biological interest is very effective because it takes only four steps to build those molecules. Moreover, it allows rapid construction of many macrocyclic derivatives around a particular theme, because it takes advantage of the fast assembly of three building blocks. Consequently, the construction of libraries of macrocyclic materials in an automated way and on solid support is a feasible task. In the present work we showed that tyrosine can introduce a lot of strain even inside rather large ring systems when the amine and the phenol groups are used as tethers. In similar cases it would be advisable to build libraries of larger macrocycles or to modify the adverse *trans* geometry of the alkene building block **5** and **22**.

Acknowledgements

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5. Ndibwami, A.; Lamothe, S.; Guay, D.; Plante, R.; Soucy, P.; Golstein, S. Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 695.
6. Tyrosine was treated with tosyl chloride and 1 M NaOH in dioxane, then NaOH in refluxing ethanol to yield Ts-Tyr-OH (57%). Diazomethane treatment in ether gave the corresponding methyl ester quantitatively. The phenol group was protected with DHP and PPTS in dichloromethane (98%) to give **4**. Finally the methyl ester was hydrolyzed with 1 M NaOH to yield **27** (99%).
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8. 1,3-Propanediol was monoprotected with DHP and PTSA (96%); the remaining alcohol was oxidized to the aldehyde using Swern conditions (96%). The resulting aldehyde was treated with the anion of triethyl phosphonoacetate to give the corresponding *trans* acrylate (99%) whose ester was reduced with DIBAH (84%). The resulting alcohol was protected by means of TBDPSCl and imidazole in THF (98%) and the THP ether was cleaved with PPTS in isopropanol at room temperature to give the alcohol **5** (98%).
9. 1,4-Butanediol was monoprotected with DHP and PTSA (73%) to give **8**.
10. 1,6-Hexanediol was monoprotected with DHP and PTSA to give **9** (61%).
11. Brillon, D.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *27*, 1131.
12. The allylic alcohol obtained after DIBAH reduction (see Ref 8) was treated with hexachloroacetone, Ph_3P and 2,6-lutidine in THF to yield the corresponding allylic chloride (87%). The THP ether was cleaved by means of PPTS in dichloromethane and methanol (1:1) to give **22** (91%).
13. The alcohol **8** was treated with MsCl and Et_3N in dichloromethane to give the corresponding mesylate quantitatively. The mesylate was transformed into the corresponding iodide by means of NaI in refluxing acetone (90% yield). The iodide was treated with sodium dimethyl malonate in THF to yield the corresponding substituted malonate (98%) whose THP ether was subsequently cleaved with PPTS in dichloromethane and methanol (3:1) to give **25** in 96% yield.
14. The alcohol **9** was transformed into the corresponding iodide with DEAD, Ph_3P and MeI in toluene (84%). Subsequent treatment of that iodide with sodium dimethyl malonate in THF yielded quantitatively the corresponding substituted malonate whose THP ether was cleaved with PPTS in dichloromethane and methanol (3:1) to give **26** in 85% yield.
15. Macrocycle **3** analytical data: ^{1}H NMR ($CDCl_3$): δ 1.03 (m, 2H), 1.25 (m, 2H), 1.42 (m, 2H), 1.65 (m, 4H), 2.43 (bs, 3H), 2.51 (m, 4H), 2.92 (m, 1H), 3.25 (m, 3H), 3.63 (s, 3H), 3.68 (s, 3H), 4.07 (t, 3H, J = 6.2 Hz), 4.32 (m, 1H), 4.85 (m, 1H), 4.94 (m, 1H), 6.78 (d, 2H, J = 8.79 Hz), 7.06 (d, 2H, J = 8.51 Hz), 7.27 (m, 2H), 7.74 (d, 2H, J = 8.24 Hz). ^{13}C NMR ($CDCl_3$): δ 21.92, 23.23, 24.93, 28.52, 28.69, 31.30, 35.29, 36.66, 48.94, 52.55, 52.70, 57.26, 63.13, 67.38, 115.23, 125.99, 127.91, 128.95, 129.58, 130.53, 131.02, 171.20, 171.88. MS (EI, 70 eV): 630 $[M+H]^+$.