Pergamon

Tetrahedron Letters 40 (1999) 5259–5262

TETRAHEDRON LETTERS

Novel Tandem "Ene-ISMS" Methodology. Efficient and Versatile Assembly of a Pseudomonic Acid C Analogue.

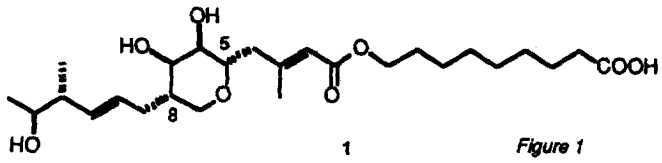
István E Markó* and Jean-Marc Plancher

Université catholique de Louvain, Département de Chimie, Laboratoire de Chimie Organique, Bâtiment Lavoisier, Place Louis Pasteur 1, B-1348, Louvain-la-Neuve, Belgium.

Received 12 April 1999; accepted 13 May 1999

Abstract: The pseudomonic acid C analogue **19** can be readily constructed using a novel tandem methodology involving, as a key-step, an ene-reaction followed by a concomitant Intramolecular Silyl-Mediated Sakurai (ISMS) cyclisation.

Pseudomonic acid C **1**, an interesting C-glycopyranoside isolated from cultures of *Pseudomonas fluorescens*, belongs to the pseudomonic acid family of antibacterial agents.[1] These natural products possess some remarkable biological properties. Not only are they particularly active against Gram positive bacteria, including *Staphylococcus aureus*, but they also display exceptional potency towards multiresistant *Staphylococcus aureus* (MRSA) strains, a serious and growing threat in most medical centres.[2] Beside its striking pharmacological properties, pseudomonic acid C also presents a challenging structure, embodying a tetrasubstituted pyran nucleus. The enhanced biological activity of **1**, coupled with its intricate architectural framework, spurred the interest of numerous research groups worldwide, resulting in several elegant total synthesis of this natural product and its congeners (Figure 1).[3]



1 *Figure 1*

Our own involvement in the pseudomonic acid family arose from the recognition that the polysubstituted tetrahydropyran nucleus of **1** might be readily assembled by an original three-component condensation reaction recently uncovered in our laboratory.[4] Our antithetic analysis of **1**, which revolves around this novel methodology, is depicted in Figure 2.

We envisioned that the C_8 side-chain (Pseudomonic acid numbering) of **1** might be introduced at a late stage in the synthesis, on the advanced ketone intermediate **2**, itself originating from oxidative cleavage of the corresponding *exo*-cyclic alkene **3**. The key methylene-tetrahydropyran **3** would then be assembled, in two simple operations, from the readily available synthons **5**, **6** and **7**. Such an approach, which entails high convergency and great flexibility, would offer a versatile and rapid access to the pseudomonic acid family and to a variety of analogues.

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00996-X

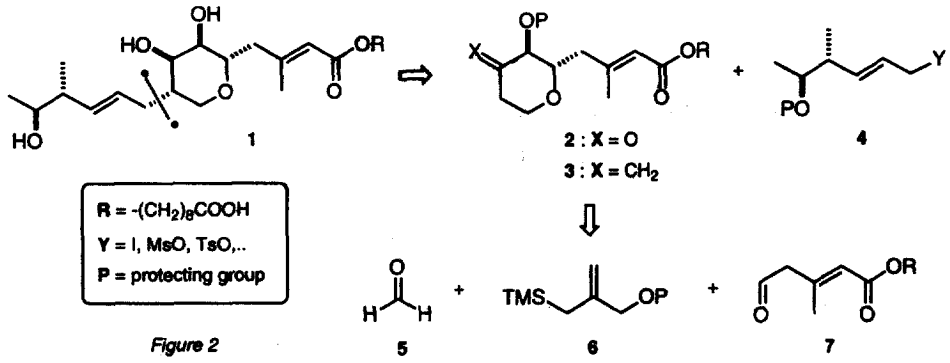


Figure 2

We have previously reported that tetrasubstituted tetrahydropyrans such as **10** could be readily constructed by a novel three-component condensation between allylsilane **9**[5] and two equivalents of aldehyde **8** (Figure 3).[4] Although the yields were modest, the pyran derivatives **10** were obtained as single diastereoisomers, possessing the 2,3-*anti*-2,6-*syn* relative stereochemistry. The transposition of this methodology to the synthesis of **1** and its derivatives would require the chemoselective and sequential pairing of two different aldehydic partners.

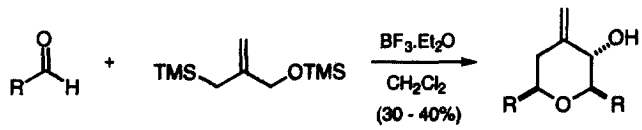


Figure 3

Whilst initial coupling experiments between the readily available annelating agent **12**[5] and various forms of formaldehyde, using a range of Lewis acids, proved fruitless, we were gratified to find that Yamamoto's aluminium reagent, MAP-H,[6] smoothly and efficiently catalysed the initial ene reaction between **12** and trioxane **11**, affording the homoallylic alcohol **13** in good yield (Figure 4)

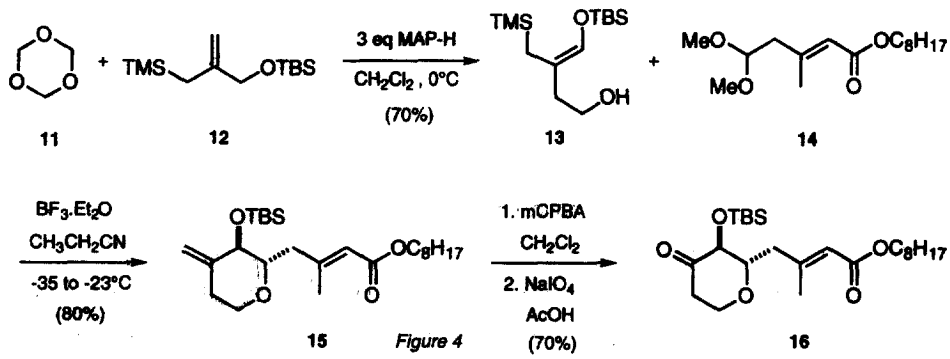


Figure 4

The subsequent ISMS condensation between (*E*)-acetal **14**[7] and alcohol **13** was successfully achieved using $BF_3.Et_2O$ in propionitrile.[8] The *exo*-methylene tetrahydropyran **15** was isolated as a single

diastereoisomer, possessing the 2,3-*trans*-stereochemistry. In contrast to what was anticipated, the oxidative cleavage of the exocyclic alkene **15** proved to be unexpectedly troublesome. For example, attempted ozonolysis of the 1,1-disubstituted olefin, under a variety of conditions, resulted in poor conversions to ketone **16**. Moreover, competitive cleavage of the conjugated enoate double bond occured as a significant side reaction. Furthermore, the *exo*-methylene substituent obstinately refused to add OsO_4 and no reaction was observed under Lemieux-Johnson type conditions.[9] The startling lack of reactivity of the exocyclic alkene **15** towards most oxidising agents might originate from the sterically hindering TBS protecting group.

We reasoned that a small oxidant, such as a peracid, would be able to thread its way through these bulky substituents and eventually functionalise the resilient olefin. Therefore, substrate **15** was treated with mCPBA in CH_2Cl_2. We were delighted to find that chemoselective epoxidation of **15** ensued, affording the desired oxirane in quantitative yield. Finally, addition of $NaIO_4$ in AcOH[10] generated the corresponding diol which underwent concomittant, *in-situ* C-C bond cleavage, delivering the long sought-after ketone **16**.

With ready access to the key-intermediate **16**, we next investigated the crucial appendage of the C_8 side-chain using the model alkylating agent **17** (Figure 5). Although the allylations usually proceeded in excellent yield, the diastereoselectivity remained unacceptably low. After considerable optimisation studies, we found that a 2:1 ratio of easily separable axial **18α** and equatorial **18β** isomers could be reached under carefully controlled conditions.

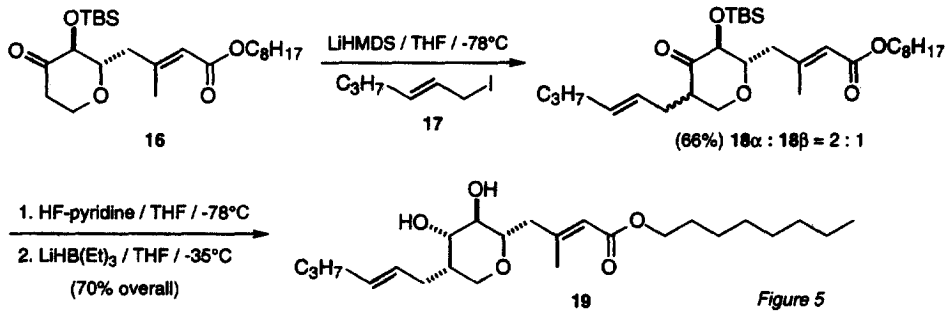


Figure 5

Finally, removal of the TBS protecting group using HF-pyridine,[11] followed by stereoselective reduction of the ketone function with lithium triethylborohydride, provided the fully functionalised model compound **19**.[12]

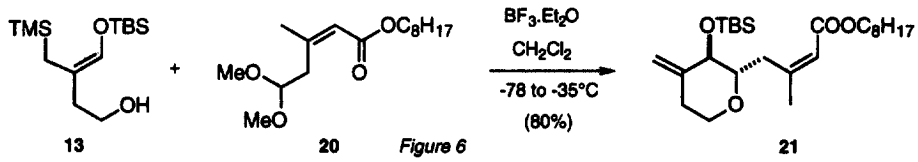
In summary, we have described a rapid and efficient (7 steps, 20% overall yield) access to the pseudomonic acid family of antibacterial agents. Our synthetic approach to model **19** involves, as a key-step, a novel tandem ene-ISMS methodology which establishes, in a single operation, the fully functionalised core of these natural products. Efforts are now underway to complete the total synthesis of pseudomonic acid C itself. The results of these investigations will be reported in due course.

Acknowledgements.

Financial support of this work by the *Université catholique de Louvain* and the *Actions de recherche concertées* (convention 96/01-197), in the form of a studentship to JMP, is gratefully acknowledged. IEM is thankful to Merck for its continuous support and for receiving the Merck Young Investigator Award.

References and Notes.

1. (a) Badder, A.; Garre, C. *Corresp.-Bl. Sweiz. Aerzte,* **1887**, *17,* 385. (b) Fuller, A.T.; Mellows, G.; Woolford, M.; Banks, G.T.; Barrow, K.D.; Chain, E.B. *Nature,* **1971**, *234,* 416. (c) Alexander, R.G.; Clayton, J.P.; Luk, K.; Rogers, N.H.; King, T.J. *J. Chem. Soc., Perkin Trans. I,* **1978**, 561.
2. (a) Hughes, J.; Mellows, G. *Biochem. J.,* **1978**, *176,* 305. (b) Clayton, J.P.; Olkivier, R.S.; Rogers, N.H.; King, T.J. *J. Chem. Soc., Perkin Trans. I,* **1979**, 838. (c) Hughes, J.; Mellows, G.; Soughton, S. *FEBS Lett.,* **1980**, *122,* 322. (d) Ward, A.; Campoli-Richards, D.M. *Drugs,* **1986**, *32,* 425.
3. (a) Kozikowski, A.P.; Schmiesing, R.J.; Sorgi, K.L. *J. Am. Chem. Soc.,* **1980**, *102,* 6577. (b) Shönenberger, B.; Summermatter, W.; Gatter, C. *Helv. Chim. Acta,* **1982**, *65,* 2333. (c) Raphael, R.A.; Stibbard, J.H.A.; Tidbury, R. *Tetrahedron Lett.,* **1982**, *23,* 2407. (d) Fleet, G.W.J.; Spensley, C.R.C. *Tetrahedron Lett.,* **1982**, *23,* 109. (e) Snider, B.B.; Phillips, G.B. *J. Am. Chem. Soc.,* **1982**, *104,* 1113. (f) Beau, J.-M.; Aburaki, S.; Pougny, J.-R.; Sinäy, P. *J. Am. Chem. Soc.,* **1983**, *105,* 621. (g) Curran, D.P.; Suh, Y.-G. *Tetrahedron Lett.,* **1984**, *25,* 4179. (h) Keck, G.E.; Kachensky, D.F.; Enholm, E.J. *J. Org. Chem.,* **1984**, *49,* 1462. (i) Kuroda, C.; Theramongkol, P.; Engebrecht, J.R.; White, J.D. *J. Org. Chem.,* **1986**, *51,* 956. (j) Bates, H.A.; Farina, J.; Tong, M. *J. Org. Chem.,* **1986**, *51,* 2637. (k) Williams, D.R.; Moore, J.L.; Yamada, M. *J. Org. Chem.,* **1986**, *51,* 3916. (l) Barrish, J.C.; Lee, H.L.; Mitt, T.; Pizzolato, G.; Bagglioni, E.G.; Uskokovic, M.R. *J. Org. Chem.,* **1988**, *53,* 4282. (m) Rao, M.V.; Nagarajan, M. *J. Org. Chem.,* **1988**, *53,* 1432. (n) Crimmin, M.J.; O'Hanlon, P.J.; Rogers, N.H.; Walkers, G. *J. Chem. Soc., Perkin Trans. I,* **1989**, 2047. (o) Crimmin, M.J.; O'Hanlon, P.J.; Rogers, N.H.; Sime, F.M.; Walkers, G. *J. Chem. Soc., Perkin Trans. I,* **1989**, 2059. (p) Forest, A.K.; O'Hanlon, P.J.; Walkers, G. *J. Chem. Soc., Perkin Trans. I,* **1994**, 2657.
4. Markó, I.E.; Bayston, D.J. *Tetrahedron Lett.,* **1993**, *34,* 6595.
5. Trost, B.M.; Chan, D.M.T.; Nanninga, N. *Org. Synth.,* **1984**, *62,* 58.
6. (a) Maruoka, K.; Conception, A.B.; Hirayama, N.; Yamamoto, H. *J. Am. Chem. Soc.,* **1990**, *112,* 7422.(b) Saito, S.; Yamamoto, H. *J. Chem. Soc., Chem. Commun.,* **1997**, 1585.
7. Acetal **14** was prepared by a one-pot, two steps protocol involving (1) the formation of the trimethylsilyl enol ester of octyl-(3-methyl)-crotonate (LDA, THF, -78°C then TMSCl) followed by (2) condensation with trimethyl orthoformate catalysed by TMSOTf. An easily separable 2:1 mixture of E/Z double bond isomers was obtained in 56% yield.
8. It is noteworthy that no reaction occured between (*E*)-acetal **14** and homoallyl alcohol **13** in CH_2Cl_2. In sharp contrast, the (*Z*)-isomer **20** underwent smooth condensation, affording the tetrahydropyran derivative **21** in 80% yield (Figure 6). We believe that the acetal substituent of (*Z*)-**20** is activated towards the ISMS cyclisation by intramolecular neighbouring group participation of the (*Z*)-ester function. The addition of a donor solvent, such as proprionitrile, presumably enhances the reactivity of (*E*)-acetal **14** by a similar, though intermolecular, mechanism.



13 20 *Figure 6* 21

9. (a) Pappo, R.; Allen, D.S.; Lemieux, R.U.; Johnson, W.S. *J. Org. Chem.,* **1956**, *21,* 478. (b) Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. *J. Org. Chem.,* **1981**, *46,* 3936.
10. (a) Okamoto, S.; Shimazaki, T.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.,* **1986**, 1352. (b) Wu, W.-L.; Wu, Y.-L. *J. Org. Chem.,* **1993**, *58,* 3586. (c) Xie, M.; Berges, D.A.; Robins, M.J. *J. Org. Chem.,* **1996**, *61,* 5178.
11. Grice, P.; Ley, S.V.; Pietruszka, J.; Osborn, H.M.I.; Priepke, H.W.M.; Warriner, S.L. *Chem. Eur. J.,* **1997**, *3,* 431.
12. The natural β-configuration of the C_7-OH substituent can be established by Luche reduction of the hydroxyketone derived from **18α**. Unfortunately, the reduction is unselective, giving a 1:1 ratio of β- and α-isomers. All new compounds were fully characterised by spectroscopic and elemental analysis. The stereochemistry of **18α**, **18β** and 7-epi-**19** was substantiated by careful analysis of their respective NMR spectra. In some cases, comparisons were also made with crystalline model compounds for which X-ray analysis unambiguously confirmed their structure including relative stereochemistry.