HETEROCYCLES, Vol. 68, No. 6, 2006, pp. 1099 - 1103. © The Japan Institute of Heterocyclic Chemistry
Received, 14th March, 2006, Accepted, 21st April, 2006, Published online, 21st April, 2006. COM-06-10733

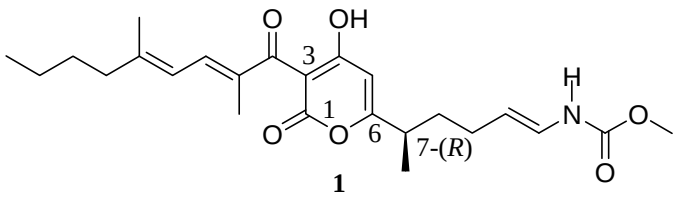
AN EFFICIENT SYNTHESIS OF (±)-MYXOPYRONIN B *VIA* VERSATILE PYRIDONE INTERMEDIATES

Ricardo Lira, Konstantinos A. Agrios, Thomas Doundoulakis, Klaus B. Simonsen, Stephen E. Webber, and Alan X. Xiang*

Department of Medicinal Chemistry, Anadys Pharmaceuticals, Inc., 3115 Merryfield Row, San Diego, CA 92121, USA

Abstract – (±)-Myxopyronin B was synthesized *via* the interconversions of pyrone and pyridone moieties. The key steps involve a BuLi-catalyzed aldol condensation and the conversion of an advanced *N*-methyl pyridone ester intermediate to the corresponding pyrone acid under basic hydrolysis.

During studies of bacterial RNA polymerase inhibitor myxopyronin B (**1**, Figure 1), we observed a unique transformation from *N*-methyl pyridone (**13**) to pyrone (**6**) *via* treatment with 1M LiOH in tetrahydrofuran. While the conversion from a pyrone to a pyridone was well documented,[1] the reaction from a pyridone to a pyrone has not been previously reported. Herein, we would like to report this finding and its usage in the total synthesis of myxopyronin B and its derivatives.



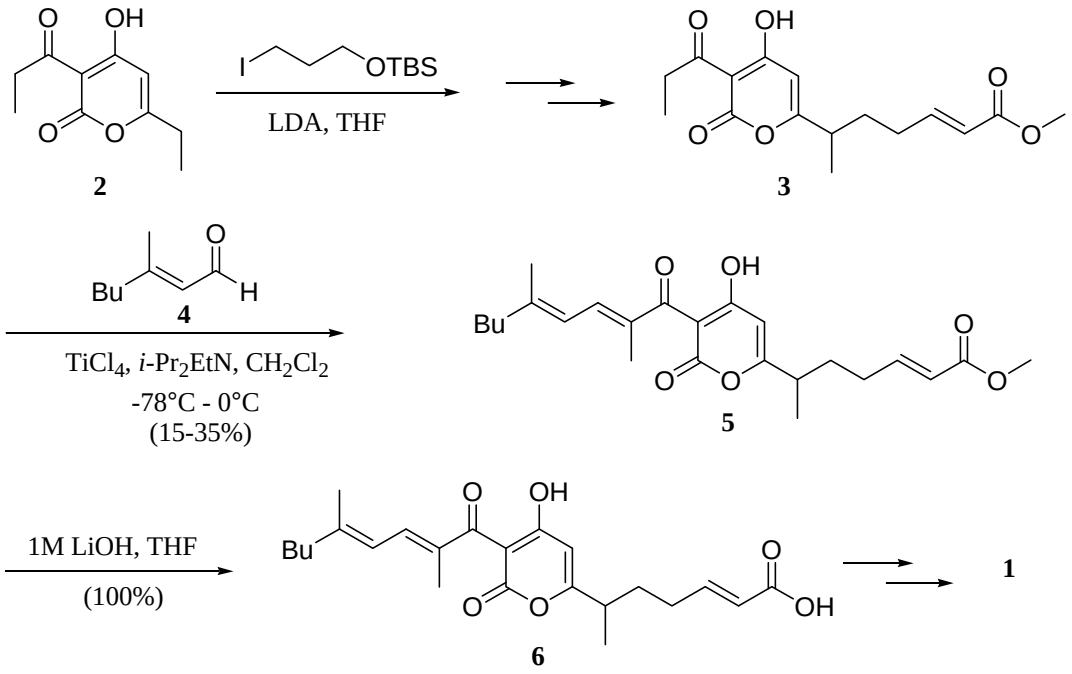
1

Figure 1

Myxopyronin B (**1**) was first isolated from the gliding bacteria *Myxococcus fulvus* Mx f50 in the early 1980s by Höfle *et al*. It belongs to an interesting class of 3-acyl-4-hydroxy-α-pyronens natural products, which also include myxopyronin A and corallopyronins A-C.[2] Myxopyronin B selectively inhibits bacterial DNA-dependent RNA polymerase[3] and represents an attractive lead for the development of antibacterial agents. DNA-dependent RNAP is the principal enzyme of transcription in all living organisms, and a key target in many regulatory pathways that control gene expression. Currently, rifampicin is the only approved drug that inhibits bacterial RNAP, but its use has been reserved due to the rapid development of resistance.[4] The exhibition of potency against rifampicin-resistant *S. aureus* by

myxopyronin B (**1**) suggests that it targets a region of RNA polymerase distinct from the one by rifampicin.

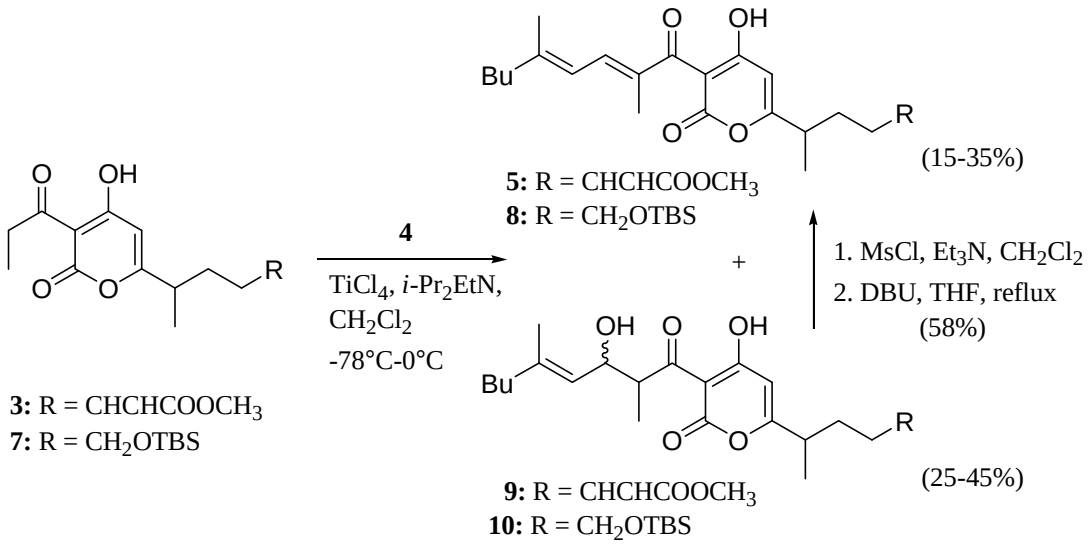
The first total synthesis of (±)-myxopyronin B (**1**) was reported in 1998 by Hu et al.[5] The synthesis makes use of a 3-propionyl-4-hydroxy-α-pyrone (**2**)[6] as the central building block from which both side chains are introduced. In that regard, an alkylation strategy was used for the installation of the right side chain followed by a titanium (IV)-promoted aldol condensation introducing the (*E*,*E*)-dienone of the left side chain. The methyl carbamate was later introduced by a modified Curtius rearrangement[7] to achieve the synthesis of (±)-myxopyronin B (**1**).



Scheme 1

During the process of synthesizing myxopyronin derivatives,[8] we encountered difficulties with the titanium (IV)-promoted aldol condensation due to the capricious nature of the dehydration step (Scheme 2). The reaction proceeded by the addition of freshly distilled $TiCl_4$ to ethyl ketone (**3**) at –78°C, followed by addition of DIPEA, generating the titanium enolate. The derived enolate was then condensed with freshly prepared *E*-3-methyl-2-heptenal (**4**). Although thin-layer chromatography analysis indicated complete condensation to the β-hydroxy ketone (**9**) within 30 min, the dehydration step proceeded poorly. The reaction was kept at –78°C for 48-56 h, however, we were unable to isolate the desired dehydrated product (**5**) in more than 15-35% yield together with a significant amount of β-hydroxy ketone (**9**) (25-45%). To improve the overall yield, we were able to convert ketone (**9**) to dienone (**5**) *via* mesylation and subsequent elimination by DBU. However, the 3-step sequence was tedious for producing a large quantity of dienone (**5**) as a common intermediate for further derivatization. While attempting to utilize

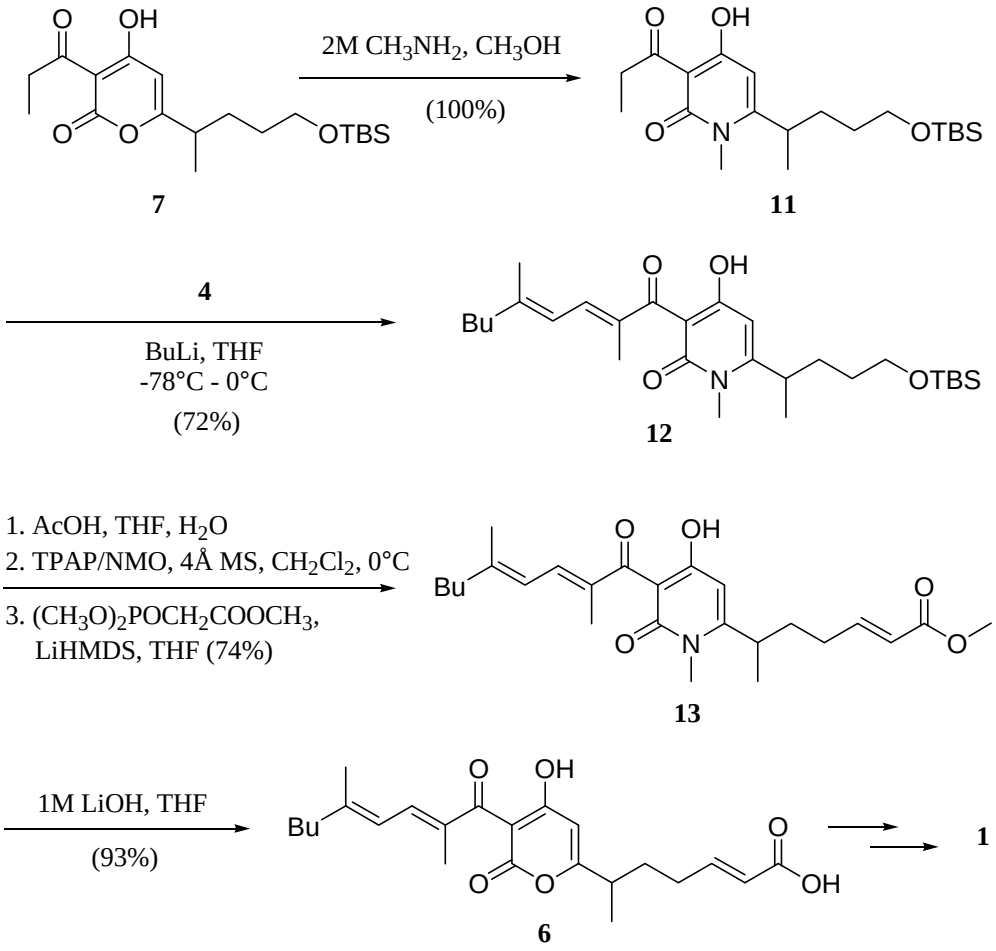
ketone (**7**)[5] as the starting material for the titanium (IV)-promoted aldol condensation (Scheme 2), we observed similar results. Clearly, a more efficient approach to construct the dienone moiety was needed.



Scheme 2

Our current synthesis takes advantage of the unique transformation from *N*-methyl pyridone (**13**) to pyrone (**6**) under basic hydrolysis. It starts from converting ketone (**7**) to its corresponding *N*-methyl pyridone (**11**) (Scheme 3). It was accomplished by treatment of **7** with excess of methylamine in methanol overnight.[1] Pyridone (**11**) was then treated with 2.2 equivalent of butyllithium (2.5 M in hexane) and 3.3 equivalent of aldehyde (**4**)[9] to generate dienone pyridone (**12**) in 72% yield. In this case, the relative stability of the pyridone core in comparison to the pyrone enabled us to apply a strong basic condition for the aldol condensation without decomposing the compound. The reaction was repeated on a multi-gram scale without incident. Dienone pyridone (**12**) was further converted to methyl ester (**13**) *via* standard synthetic transformations. *N*-methyl pyridone (**13**) was then converted to its corresponding pyrone under basic hydrolysis. Spectral data of the resulting pyrone was identical to that of compound (**6**) based on published procedure. **6** was finally subjected to the modified Curtius rearrangement[7] to afford (±)-myxopyronin B (**1**) based on published procedure.

In summary, a unique transformation from *N*-methyl pyridone (**13**) to pyrone (**6**) was discovered. While the mechanism and the scope of this transformation are still under investigation, it enabled us to synthesize (±)-myxopyronin B (**1**) and its analogs in large quantities, thus facilitating their biological evaluations.



Scheme 3

REFERENCES AND NOTES

1. For examples see: S. Castillo, H. Ouadahi, and V. Herault, *Bull. Soc. Chim. Fr.*, 1982, **2**, 257; W. C. Groutas, M. A. Stanga, M. J. Brubaker, T. L. Huang, M. K. Moi, and R. T. Carroll, *J. Med. Chem.*, 1985, **28**, 1106; H. Kherfi, M. Hamdi, and V. Speziale, *J. Heterocycl. Chem.*, 1990, **27**, 1401; A. E. Kihel, M. Benchidmi, E. M. Essassi, P. Bauchat, and R. Danion-Bougot, *Synth. Commun.*, 1999, **29**, 2435.
2. W. Kohl, H. Irschik, H. Reichenbach, and G. Höfle, *Liebigs Ann. Chem.*, 1983, 1656; W. Kohl, H. Irschik, H. Reichenbach, and G. Höfle, *Liebigs Ann. Chem.*, 1984, 1088; R. Jansen, H. Irschik, H. Reichenbach, and G. Höfle, *Liebigs Ann. Chem.*, 1985, 822.
3. H. Irschik, K. Gerth, G. Höfle, W. Kohl, and H. Reichenbach, *J. Antibiot.*, 1983, **36**, 1651.
4. E. A. Campbell, A. Korzheva, A. Mustaev, K. Murakami, S. Nair, A. Goldfarb, and S. Darst, *Cell*, 2001, **104**, 901; For other inhibitors of RNAP see: I. Artsimovitch, C. Chu, A. S. Lynch, and R. Landick, *Science*, 2003, **302**, 650.
5. T. Hu, J. V. Schaus, K. Lam, M. G. Palfreyman, M. Wuonola, G. Gustafson, and J. S. Panek, *J. Org. Chem.*, 1998, **63**, 2401.

6. Pyrone (**2**) was prepared from commercially available ethyl 3-oxopropanoate see: L. Cook, B. Ternai, and P. Ghosh, *J. Med. Chem.*, 1987, **30**, 1017.
7. L. Overman, G. Taylor, C. Petty, and P. Jessup, *J. Org. Chem.*, 1978, **43**, 2164.
8. T. Doundoulakis, A. X. Xiang, R. Lira, K. A. Agrios, S. E. Webber, W. Sisson, R. M. Aust, A. M. Shah, R. E. Showalter, J. R. Appleman, and K. B. Simonsen, *Bioorg. Med. Chem. Lett*., 2004, **14**, 5667.
9. Aldehyde (**4**) was freshly prepared from methyl 2-butynoate in a three-step reaction sequence: (i) methyl 2-butynoate, BuLi, CuI; (ii) $LiAlH_4$; (iii) TPAP, NMO see: R. J. Anderson, V. L. Corbin, G. Cotterrell, G. R. Cox, C. A. Henrick, F. Schaub, and J. B. Siddall, *J. Am. Chem. Soc.*, 1975, **97**, 1197; K. Ogura, T. Nishino, T. Koyama, and S. Seto, *J. Am. Chem. Soc.*, 1970, **92**, 6036.