Pergamon

Tetrahedron Letters 42 (2001) 6061–6064

TETRAHEDRON LETTERS

Alternative synthesis and thermal atropisomerism of a fully functionalized DEFG ring system of teicoplanin

Yoshiki Mori, J. Jeffrey McAtee, Olivier Rogel and Dale L. Boger*

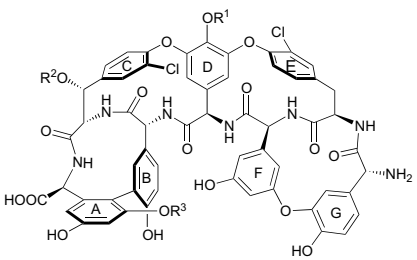
Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Received 30 June 2001; accepted 6 July 2001

Abstract—An alternative synthesis and the thermal atropisomerism of a fully functionalized DEFG ring system of teicoplanin are described.

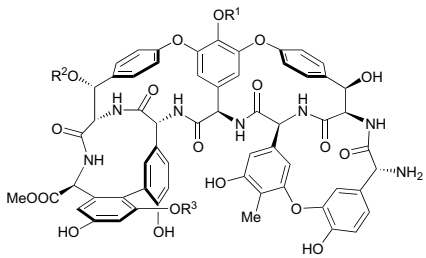
1. Introduction

Teicoplanin (**1**)[1,2] is a complex of five closely related glycopeptides isolated from *Actinoplanes teichomyceticus* (ATCC 31121) that belongs to the ristocetin (**2**)[3–6] family. Teicoplanin and vancomycin (**3**)[7–12] are clinically useful drugs which are used as a last resort for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[10] However, the first report of vancomycin-resistant *enterococci* appeared in 1988 and the incidence is increasing.[12] These antibiotics incorporate the identical ABCD ring system, but teicoplanin and ristocetin possess an additional 14-membered FG ring system[13,14] not found in vancomycin, making them even more challenging synthetic targets than vancomycin.[15]

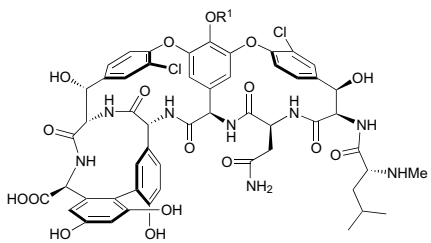


Teicoplanin (**1**)
R^1, R^2 and R^3 = sugar units

We recently reported first and second generation total syntheses of the teicoplanin aglycon[16] incorporating the common vancomycin/teicoplanin ABCD ring system as a key intermediate which was first prepared in the course of a total synthesis of the vancomycin aglycon.[17] Thus, precursors of the teicoplanin DEFG ring system were coupled with the common ABCD ring system followed by diaryl ether macrocyclization of the DE ring system enlisting a phenoxide aromatic nucleophilic substitution reaction of an *o*-fluoronitroaromatic.[18] In the course of these studies, we observed substantial variations in the level of kinetic atropisomer diastereoselection achieved in the closure of the teicoplanin DE ring system which depended on the substrate structure (Fig. 1). Thus, closures of **4**, **5** and **6**



Ristocetin (**2**)
R^1, R^2 and R^3 = sugar units



Vancomycin (**3**)
R^1 = sugar unit

* Corresponding author. Fax: +1-858-784-7550; e-mail: boger@scripps.edu

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01199-6

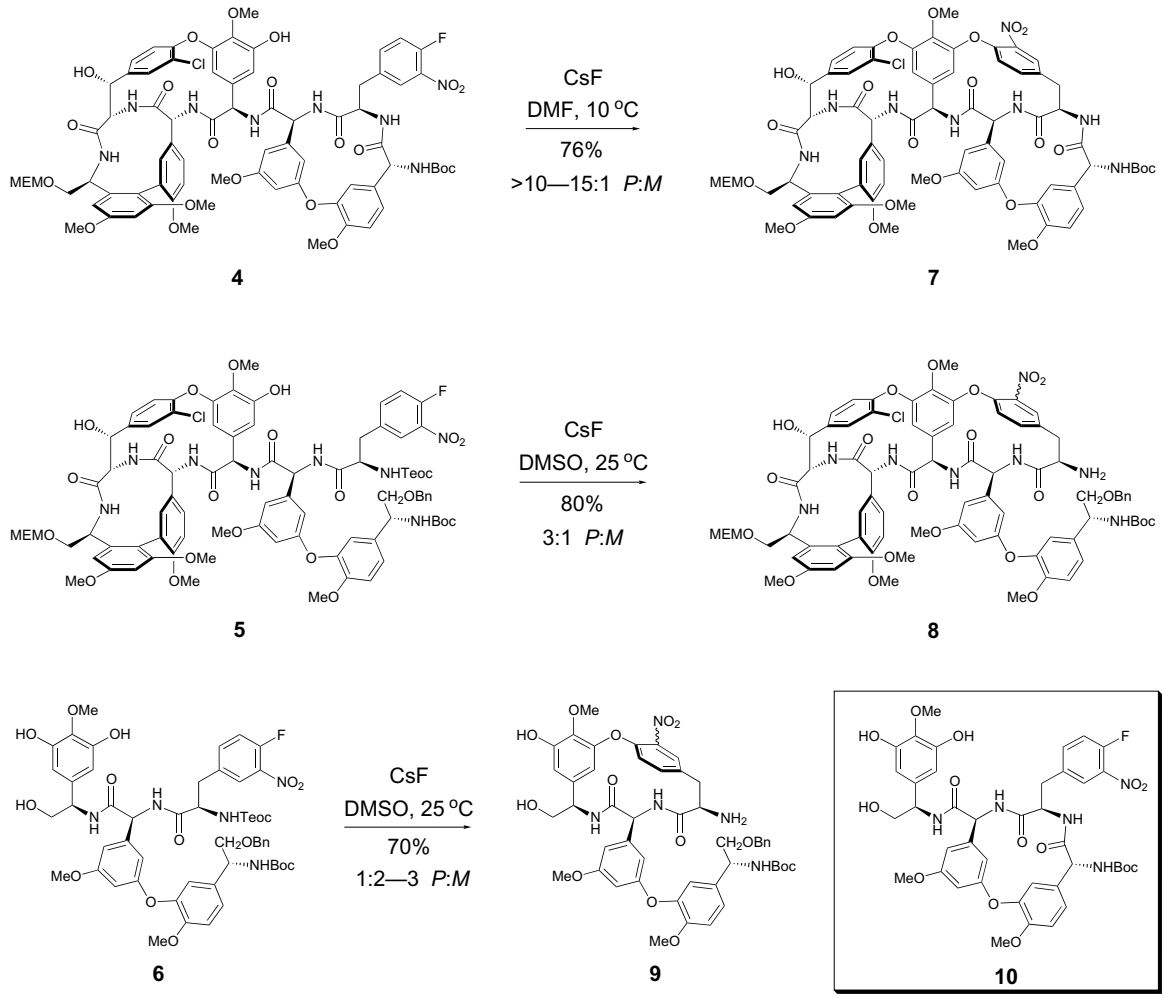
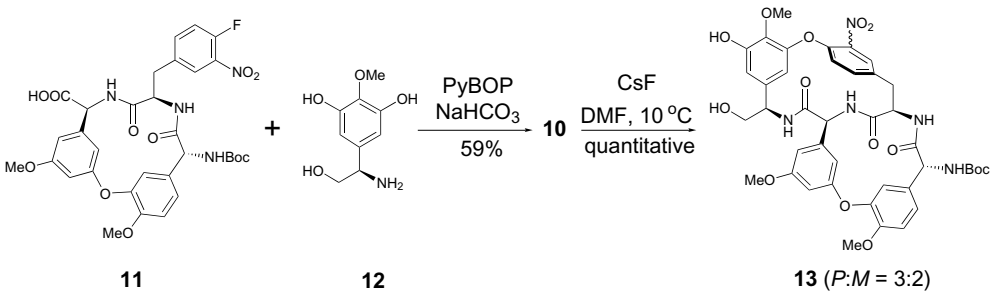


Figure 1.

induced by treatment with CsF provided the macrocyclization products **7**, **8** and **9** in superb yields, but with widely different atropisomer preferences.[16] Notably, the diastereoselection of the ring closure was superb employing the substrate **4** with the FG ring system intact and favored the natural atropisomer stereochemistry (>10–15:1).[16] The diastereoselection was lower (3:1) and the ring closure was slower with the substrate **5** containing an acyclic FG ring system precursor, but still favored the natural atropisomer stereochemistry. The comparable closure of **6** on the other hand, which also lacks the attached ABCD ring system, proceeded with a weak preference for the unnatural DE atropisomer (1:2–3). These results indicate that both the intact ABCD ring system and especially the preformed FG ring system influence both the ease of ring closure and the kinetic diastereoselection. Consequently, we subsequently became interested in the relative ease and potential kinetic diastereoselection of the analogous ring closure of the untested substrate **10** versus **6** for the preparation of the isolated teicoplanin DEFG ring system. Herein, we report the results of these studies.



Scheme 1.

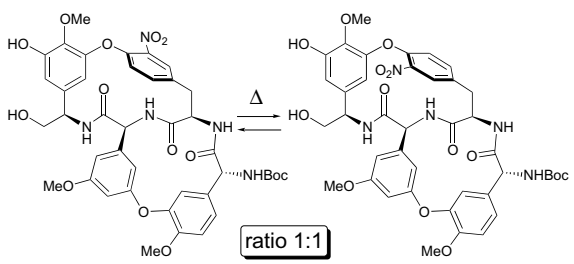
2. Results and discussion

The substrate required to study this closure of the teicoplanin DE ring system was easily assembled from existing precursors. The carboxylic acid **11**, corresponding to the intact EFG ring system of teicoplanin which was prepared in our preceeding studies,[16] was coupled with free amine **12**[19] (PyBOP, DMF, $NaHCO_3$, −58°C, 2 h, 59%) providing the key substrate **10** (Scheme 1). The use of the free D ring amino alcohol versus the ester precludes potential epimerization of the C_2[4] center under the conditions of macrocyclization.[19,20] The macrocyclization of **10** occurred with a facility that exceeded that of **6** lacking the preformed FG ring system. Thus, treatment of **10** with CsF (100 equiv, DMF, 10°C, 24 h) provided a quantitative conversion to a 3:2 mixture of the separable *P*- and *M*-**13** favoring the natural stereochemistry.[21] By contrast, the closure of **6**, which lacked the preformed FG ring system, required the use of DMSO versus DMF as solvent and a reaction temperature of 25°C for effective macrocyclization. Thus, both the facility of ring closure and the atropisomer diastereoselection improved (3:2 versus 1:2–3) with the substrate **10** versus **6**.

We also examined the thermal isomerism of the atropisomers (Scheme 2). The unnatural *M*-atropisomer could be rapidly equilibrated to a 1:1 mixture of *M*:*P* atropisomers thus permitting recycling to the natural stereochemistry. Consistent with prior observations, this occurred with an experimental E_a of 22.9 kcal/mol which was analogous to, but slightly lower than the corresponding chloride (E_a = 23.3 kcal/mol)[16] and greater than **9** lacking the preformed FG ring system (E_a = 16.2–17.2 kcal/mol).[16]

Acknowledgments

We gratefully acknowledge the financial support of the National Institutes of Health (CA 41101), The Skaggs Institute for Chemical Biology, the sabbatical leave of Y.M. (Mitsubishi-Tokyo Pharmaceuticals, Inc. 1999–2001), and the award of a NIH postdoctoral fellowship to J.J.M. (AI10367)



P—13 *M*—13

k_{obs}^{130} (h^{-1}) = 0.19, $t_{1/2}$ (h) = 1.54
k_{obs}^{140} (h^{-1}) = 0.38, $t_{1/2}$ (h) = 0.77
E_a = 22.9 kcal/mol
$\Delta H^{\ddagger}$ = 22.1 kcal/mol, $\Delta S^{\ddagger}$ = —7.6 eu.

Scheme 2.

References

1. Parenti, F.; Beretta, G.; Berti, M.; Arioli, V. *J. Antibiot.* **1978**, *31*, 276.
2. (a) Hunt, A. H.; Molloy, R. M.; Occolowitz, J. L.; Marconi, G. G.; Debono, M. *J. Am. Chem. Soc.* **1984**, *106*, 4891; (b) Barna, J. C. J.; Williams, D. H.; Stone, D. J. M.; Leung, T.-W. C.; Doddrell, D. M. *J. Am. Chem. Soc.* **1984**, *106*, 4895.
3. Grundy, W. E.; Sinclair, A. C.; Theriault, R. J.; Goldstein, A. W.; Rickher, C. J.; Warren, H. B.; Oliver, T. J.; Sylvester, J. C. *Antibiot. Annu.* **1956–1957**, 687.
4. Philip, J. E.; Schenck, J. R.; Hargie, M. P. *Antibiot. Annu.* **1956–1957**, 699.
5. Sztaricskai, F.; Harris, C. M.; Neszmelyi, A.; Harris, T. M. *J. Am. Chem. Soc.* **1980**, *102*, 7093.
6. Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 363.
7. McCormick, M. H.; Stark, W. M.; Pittenger, G. E.; Pittenger, R. C.; McGuire, J. M. *Antibiot. Annu.* **1955–1956**, 606.
8. (a) Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915; (b) Sheldrick, G. M.; Jones, P. G.; Kennard, O.; Williams, D. H.; Smith, G. A. *Nature* **1978**, *271*, 223; (c) Williams, D. H.; Kalman, J. R. *J. Am. Chem. Soc.* **1977**, *99*, 2768; (d) Williamson, M. P.; Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 6580.
9. Malabarba, A.; Nicas, T. I.; Thompson, R. C. *Med. Res. Rev.* **1997**, *17*, 69.
10. Wiedemann, B.; Grimm, H. In *Antibiotics in Laboratory Medicine*; Lorian, V., Ed.; Williams and Wilkins: Baltimore, MD, 1996; pp. 900–1168.
11. Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172.
12. Walsh, C. T.; Fisher, S. L.; Park, I.-S.; Prahalad, M.; Wu, Z. *Chem. Biol.* **1996**, *3*, 21.
13. Chakraborty, T. K.; Reddy, G. V. *J. Org. Chem.* **1992**, *57*, 5462.
14. (a) Pearson, A. J.; Shin, H. *J. Org. Chem.* **1994**, *59*, 2314; (b) Pearson, A. J.; Belmont, P. O. *Tetrahedron Lett.* **2000**, *41*, 1671.
15. Reviews: (a) Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096; (b) Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135
16. (a) Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J.-H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862; (b) Boger, D. L.; Kim, S. H.; Miyazaki, S.; Strittmatter, H.; Weng, J.-H.; Mori, Y.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 7416.
17. Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004; Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 3226; For related and preceeding efforts, see: Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew.*

Chem., *Int*. *Ed*. *Engl*. **1998**, *37*, 2704; Nicolaou, K. C.; Natarajan, S.; Li, H.; Jain, N. F.; Hughes, R.; Solomon, M. E.; Ramanjulu, J. M.; Boddy, C. N. C.; Takayanagi, M. *Angew*. *Chem*., *Int*. *Ed*. *Engl*. **1998**, *37*, 2708.

18. Zhu, J. *Synlett* **1997**, 133.
19. (a) Boger, D. L.; Castle, S. L.; Miyazaki, S.; Wu, J. H.; Beresis, R. T.; Loiseleur, O. *J*. *Org*. *Chem*. **1999**, *64*, 70; (b) Boger, D. L.; Beresis, R. T.; Loiseleur, O.; Wu, J. H.; Castle, S. L. *Bioorg*. *Med*. *Chem*. *Lett*. **1998**, *8*, 721; (c) Boger, D. L.; Loiseleur, O.; Castle, S. L.; Beresis, R. T.; Wu, J. H. *Bioorg*. *Med*. *Chem*. *Lett*. **1997**, *7*, 3199; (d) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J*. *Org*. *Chem*. **1997**, *62*, 4721; (e) Boger, D. L.; Borzilleri, R. M.; Nukui, S. *J*. *Org*. *Chem*. **1996**, *61*, 3561; (f) Boger, D. L.; Borzilleri, R. M.; Nukui, S. *Bioorg*. *Med*. *Chem*. *Lett*. **1995**, *5*, 3091.
20. (a) Boger, D. L.; Weng, J.-H.; Miyazaki, S.; McAtee, J. J.; Castle, S. L.; Kim, S. H.; Mori, Y.; Rogel, O.; Strittmatter, H.; Jin, Q. *J*. *Am*. *Chem*. *Soc*. **2000**, *122*, 10047; (b) Pearson, A. J.; Hunwoo, D. S. *J*. *Org*. *Chem*. **1994**, *59*, 2314; (c) Barna, J. C. J.; Williams, D. H. *J*. *Antibiot*. **1984**, *37*, 1204.
21. For **10**: $[\alpha]_{25}^{D}$ −14 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD, 400 MHz): δ (8.03 (dd, J=2.4, 7.4 Hz, 1H), 7.60 (m, 1H), 7.31 (t, J=7.9 Hz, 1H), 7.22 (dd, J=2.0, 8.5 Hz, 1H), 7.18 (d, J=8.5 Hz, 1H), 6.99 (d, J=2.1 Hz, 1H), 6.64 (t, J=2.0 Hz, 1H), 6.58 (brs, 1H), 6.31 (brs, 1H), 6.29 (brs, 2H), 5.33 (brs, 1H), 5.02 (brs, 1H), 4.63 (m, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.71 (s, 4H), 3.65–3.62 (m, 2H), 3.10–3.03 (m, 2H), 1.40 (s, 9H); MALDIFTMS (DHB) m/z 872.2753 ($M+Na^+$, $C_{41}H_{44}FN_5O_{14}$ requires 872.2761). For: *P*-**13** (60% yield): $[\alpha]_{25}^{D}$ −24 (*c* 0.02, MeOH); ^{1}H NMR (CD_3OD, 500 MHz): δ (7.90 (s, 1H), 7.77 (d, J=7.7 Hz, 1H), 7.27–7.24 (m, 2H), 7.15 (d, J=8.5 Hz, 1H), 7.14 (d, J=1.9 Hz, 1H), 6.74 (brs, 1H), 6.64 (t, J=1.9 Hz, 1H), 6.43 (d, J=1.9 Hz, 1H), 6.19 (brs, 1H), 5.54 (brs, 1H), 5.27 (s, 1H), 4.99 (brs, 1H), 4.23 (brs, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.71–3.68 (m, 2H), 3.41 (brs, 1H), 3.09–3.03 (m, 2H), 1.46 (s, 9H); MALDIFTMS (DHB) m/z 852.2707 ($M+Na^+$, $C_{41}H_{43}N_5O_{14}$ requires 852.2699). For: *M*-**13** (40% yield): $[\alpha]_{25}^{D}$ −21 (*c* 0.02, MeOH); ^{1}H NMR (CD_3OD, 400 MHz): δ (8.21 (s, 1H), 7.53 (d, J=7 Hz, 1H), 7.28–7.24 (m, 2H), 7.20–7.13 (m, 2H), 6.69 (s, 1H), 6.65 (brs, 1H), 6.43 (d, J=1.9 Hz, 1H), 6.21 (brs, 1H), 5.59 (brs, 1H), 5.29 (s, 1H), 4.98 (brs, 1H), 4.23 (brs, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 3.79 (s, 3H), 3.71–3.68 (m, 2H), 3.41 (brs, 1H), 3.09–3.03 (m, 2H), 1.46 (s, 9H); MALDIFTMS (DHB) m/z 852.2697 ($M+Na^+$, $C_{41}H_{43}N_5O_{14}$ requires 852.2699).