Pergamon

Tetrahedron Letters 42 (2001) 215–218

TETRAHEDRON LETTERS

Total synthesis of (+)-epopromycin B and its analogues—studies on the inhibition of cellulose biosynthesis

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Received 27 October 2000; accepted 2 November 2000

Abstract—The described inhibition of the cellulose biosynthesis by epopromycin B prompted us to establish a short and efficient synthesis of the natural product, suitable for accessing a broad range of unnatural analogues in a multiparallel fashion. During the course of our synthesis the absolute configuration of (+)-epopromycin B could be determined.

Epopromycin A (**1**) and B (**2**) (Fig. 1) are fermentation products that were isolated from a *Streptomycete* by *Tatsuta* and co-workers.[1] The metabolites were found on the basis of their biological activity, the inhibition of the cell-wall synthesis of plant protoplasts.[1] To confirm this interesting herbicidal activity and to explore its mode of action, we aimed to establish a total synthesis of epopromycin B (**2**), as well as suitable derivatives and analogues.

The most intriguing structural feature of **1** and **2** is the β-hydroxy-α-epoxyketone terminus, which is also found in the proteasome inhibitors TMC-86 and TMC-96,[2] as well as in the angiostatic natural product eponemycin.[3] We proposed that this common structural motif may represent the toxophore, and decided to conserve it, but to investigate the activity of both epoxy epimers during the course of our SAR studies. This would also allow us to establish the C-2 stereo-

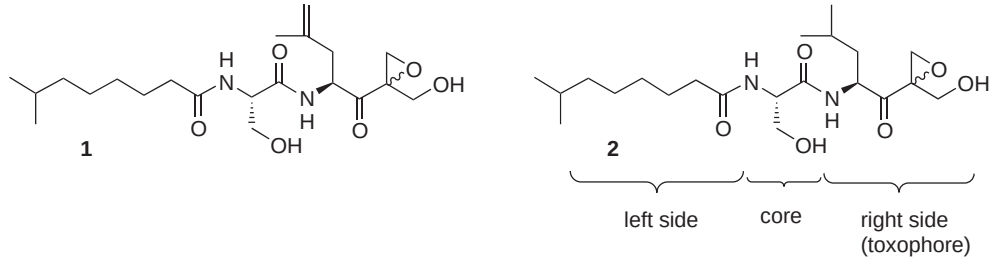
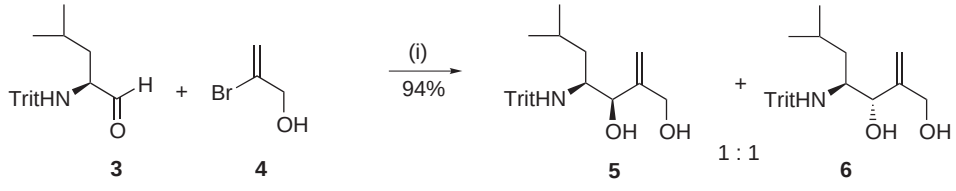


Figure 1. Epopromycin A (**1**) and B (**2**).



Scheme 1. *Reagents:* (i) *t*BuLi, THF, −78°C, 2 h.

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0040-4039/01/$ - see front matter
PII: S0040-4039(00)01944-4

chemistry of the natural product **2**, which is so far unknown.

Our synthetic approach was influenced by the previously reported strategies for the synthesis of eponemycin.[4–6] We envisaged a multiparallel synthesis using stable and easily accessible building blocks and without chromatographic purification after the final coupling step. The results are outlined in the following schemes.

The most challenging task was to establish a high yielding access to the right side building block in both C-2-epimeric forms and with assigned stereochemistry. The chosen sequence starts with the addition of a vinyl lithium species derived from 2-bromo-1-hydroxy-2-propene[7,8] (**4**) to aldehyde (**3**), providing an easily separable mixture of the epimeric alcohols **5** and **6** in 93% yield (Scheme 1).[9]

Regioselective silylation of the terminal hydroxyl group of **5** was followed by deprotection of the amino group.[10] The configuration of the obtained amino alcohol **7** was determined via its oxazolidinone derivative **8** by analyzing its ^{1}H NMR shifts and coupling constants (Scheme 2).[11]

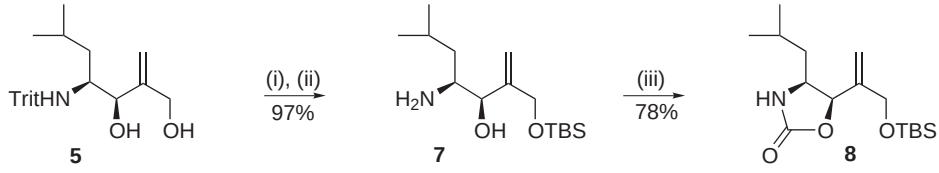
The amino alcohol **7** was reprotected as its FMOC-derivate **9**. Epoxidation with *m*CPBA led to a nearly 1:1 mixture of oxiranes **10** and **11**, column chromatographic separation and deprotection under mild conditions afforded the desired epoxy diols **12** and **13** in high overall yield (Scheme 3).

In order to verify the C-2 configuration of **13**, its precursor **10** was synthetically linked to the known compound **14**[4] (Scheme 3). Correlation of the spectroscopic data of **14** with the published ones established the C-2 stereochemistry of **10** and **11**, respectively.

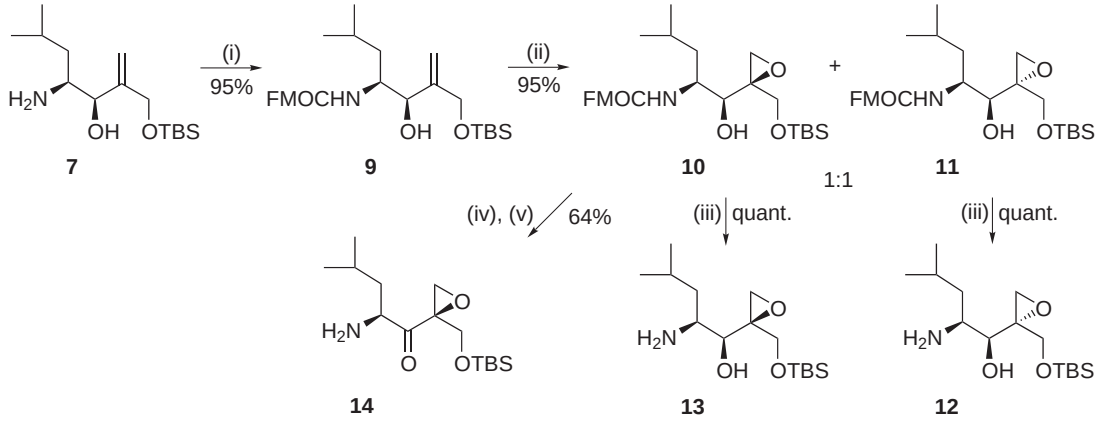
We then turned our attention towards the preparation of the left side fragment. The required isononanic acid[12] (**15**) was synthesized by Wittig reaction and hydrogenation over Pd/C starting from 5-bromo-methylpentanoate (**16**) (Scheme 4).

DCC mediated coupling of **15** with serine methylester (**18**), followed by silylation and mild saponification gave the desired 'left side-core'-fragment **19** of epopromycin B (**2**) (Scheme 5).

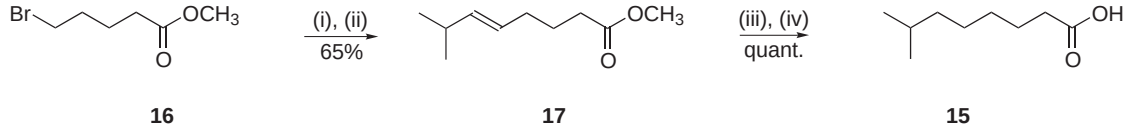
The final coupling of **19** with each of the amino epoxides **12** or **13**, was achieved using DCC and *N*-hydroxysuccinimide. IBX oxidation and deprotection of the



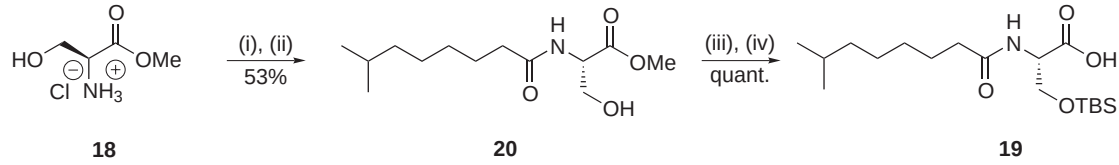
Scheme 2. *Reagents:* (i) TBSCl, DMF, imidazole, rt; (ii) AcOH, rt; (iii) (imidazole)$_2$CO, NaH, DMF, rt.



Scheme 3. *Reagents:* (i) FMOCCl, DMF, Hünig's base; (ii) *m*CPBA, CH_2Cl_2, rt; (iii) triethylamine, CH_2Cl_2, rt; (iv) IBX, DMSO, rt; (v) triethylamine, CH_2Cl_2, −20°C.

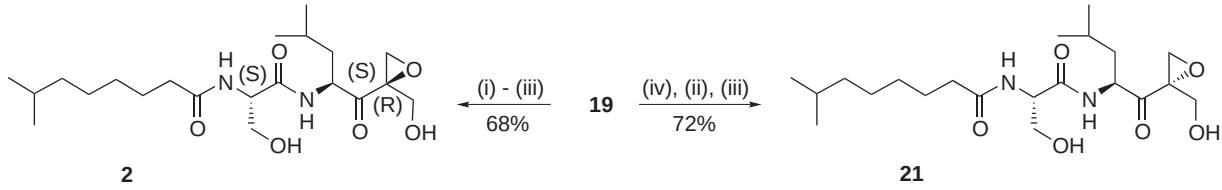


Scheme 4. *Reagents:* (i) Ph_3P, CH_3CN; (ii) NaH, *i*PrCHO; (iii) K_2CO_3, MeOH; (iv) H_2, Pd/C, EtOH.



18 20 19

Scheme 5. *Reagents:* (i) NH_3, CH_2Cl_2; (ii) DCC, CH_2Cl_2, **15**; (iii) TBSCl, DMF, imidazole; (iv) LiOH, H_2O, MeOH.



2 21

Scheme 6. *Reagents:* (i) DCC, *N*-hydroxysuccinimide, **13**, CH_2Cl_2, −20°C, 4 h; (ii) IBX, DMSO, rt, 8 h; (iii) HF, CH_3CN, 0°C, 2 h; (iv) DCC, *N*-hydroxysuccinimide, **12**, CH_2Cl_2, −20°C, 4 h.

crude products led after a liquid–liquid extraction to pure epopromycin B (**2**) and its C-2 epimer (**21**) in about 70% yield (Scheme 6).

In addition, following the above protocol more then 15 different epopromycin B analogues were synthesized in both C-2-epimeric forms. None of them showed any significant inhibition of the biosynthesis of cellulose[13] except for the natural product itself, for which an I_{50} of 7.6 μmol l^{-1} was measured. The C-2-epimer **21** was also found to be inactive. However, some of the analogues expressed pronounced antifungal activity against various phytopathogens.

In conclusion a total synthesis of (+)-epopromycin B (**2**), its C-2-epimer **21**, and more then 30 unnatural analogues has been established.[14] Since the approach is based on the utilization of the (*2S*)- and (*2R*)-epoxide intermediates (**13** and **12**) the absolute configuration of the natural and the unnatural metabolite was determined as shown in Scheme 6.

Acknowledgements

The author thanks Dr. K. Kreuz (Novartis Crop Protection AG, Basel) for the measurement of the cellulose biosynthesis inhibition of the prepared compounds.

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9. Other common *N*-protecting groups used to block the amino substituent, led to the formation of alkyne side products (30–50%) via elimination of the vinyl bromide prior to the addition.
10. In the following only the reactions for **5** are shown. However, the demonstrated chemistry works as well for **6**. Both epimers can be used, since the distinguishing stereochemical center collapses during the IBX oxidation.
11. Kano, S.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem*. **1989**, *54*, 513–515. The 4-H and 5-H signals (^{1}H, 400 MHz, $CDCl_3$) of **8** (*cis*) and its *trans* isomer are as follows: **8** (*cis*): δ 3.81 (ddd, $J = 11.3$, 7.9, 3.8 Hz, 4-H), 5.18 (d, $J = 7.9$ Hz, 5-H); (*trans*): δ 3.72 (ddd, $J = 9.0$, 5.8, 4.9 Hz, 4-H), 4.71 (d, $J = 5.8$ Hz, 5-H).
12. Davidson, B. S.; Schumacher, R. W. *Tetrahedron* **1993**, *49* (30), 6569–6574.
13. The assay is based on the incorporation of ^{14}C from [^{14}C]glucose into acid-insoluble cellulose in a tomato cell suspension culture.
14. All new compounds were completely characterized and gave satisfactory spectral and analytical data. Selected data:
Compound **7**: ^{1}H NMR δ 5.23 (s, 1H), 5.15 (s, 1H), 4.19–4.30 (m, 2H), 3.98 (d, $J = 5.5$ Hz, 1H), 2.98 (m, 1H), 2.1 (s_{br}, 2H), 1.75 (m, 1H), 1.40 (m, 1H), 1.20 (m, 1H), 0.97 (d, $J = 6.4$ Hz, 3H), 0.95 (s, 9H), 0,91 (d, $J = 5.3$ Hz, 3H), 0.12 (s, 6); ES-MS m/z 288 (M^{+1}).
Compound **9**: ^{1}H NMR δ 7.79 (d, $J = 7.8$ Hz, 2H), 7.61 (d, $J = 7.3$ Hz, 2H), 7.42 (tm, $J = 7.3$ Hz, 2H), 7.32 (tm, $J = 7.4$ Hz, 2H), 5.19 (s, 1H), 5.12 (s, 1H), 4.45 (m, 2H), 4.18–4.32 (m, 4H), 3.92 (m, 1H), 2.91 (d, $J = 5.5$ Hz, 1H), 1.60 (m, 1H), 1.34–1.40 (m, 2H), 0.94 (m, 15H), 0.13 (s, 3H), 0.12 (s, 3H); ES-MS m/z 510 (M^{+1}).

Compound **12**: ^{1}H NMR δ 3.96 (d, $J = 11.1$ Hz, 1H), 3.52 (d, $J = 11.1$ Hz, 1H), 3.17 (d, $J = 6.9$ Hz, 1H), 2.91 (ddd, $J = 10.0$, 6.9, 2.7 Hz, 1H), 2.77 (d, $J = 4.7$ Hz, 1H), 2.74 (d, $J = 4.7$ Hz, 1H), 1.68 (m, 1H), 1.37 (m, 1H), 1.15 (m, 1H), 0.81 (m, 15H), 0.0 (s, 3H), −0.02 (s, 3H); ES-MS m/z 304 (M^{+1}).

Compound **13**: ^{1}H NMR δ 3.82 (d, $J = 11.6$ Hz, 1H), 3.60 (d, $J = 11.6$ Hz, 1H), 3.60 (m, 1H), 2.91 (ddd, $J = 9.8$, 6.7, 2.8 Hz, 1H), 2.82 (d, $J = 4.7$ Hz, 1H), 2.71 (d, $J = 4.7$ Hz, 1H), 1.71 (m, 1H), 1.10–1.35 (m, 1H), 0.82 (d, $J = 6.7$ Hz, 3H), 0.82 (m, 12H), 0.0 (s, 3H), −0.02 (s, 3H); ES-MS m/z 304 (M^{+1}).

Compound **21**: ^{1}H NMR δ 7.31 (d, $J = 7.2$ Hz, NH), 6.62 (d, $J = 7.4$ Hz, NH), 4.62 (dd, $J = 11.8$, 6.1 Hz, 1H), 4.41 (m, 1H), 4.23 (d, $J = 12.2$ Hz, 1H), 3.94 (dd, $J = 11.0$, 3.5 Hz, 1H), 3.57 (dd, $J = 11.0$, 6.1 Hz, 1H), 3.51 (d, $J = 12.2$ Hz, 1H), 3.37 (m, 1H), 2.96 ($J =$ d, 4.7 Hz, 1H), 2.91 (d, $J = 4.7$ Hz, 1H), 2.17 (m, 2H), 1.86 (m, 1H), 1.08–1.64 (m, 12 H), 0.84 (s, 3H), 0.82 (s, 3H), 0.78 (s, 3H), 0.77 (s, 3H); ES-MS m/z 415 (M^{+1}), 437 (M^{+Na}).