A Concise and Efficient Stereoselective Synthesis of the C1–C11 Fragment of Macrolactin A

Carlo Bonini,*[a] Lucia Chiummiento,[a] Valeria Videtta,[a] Françoise Colobert,[b] Guy Solladié[b]

[a] Dipartimento di Chimica, Università degli Studi della Basilicata, via N. Sauro 85, 85100 Potenza, Italy
Fax +39(971)202223; E-mail: bonini@unibas.it

[b] Laboratoire de Stéréochemie associé au CNRS, Université Louis Pasteur (ECPM), rue Bacquerel, 67087 Strasbourg, France

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Abstract: A stereoselective synthesis of the C1–C11 fragment of macrolactin A, using original approaches for the introduction of the *Z*,*E*-diene stereochemistry and the C-7 stereogenic center, is reported. The adopted strategy has allowed us to build up the fragment by the assembly of three key intermediates via cross-metathesis, Still–Gennari, and Wittig olefinations. Opening of the commercially available chiral benzyl glycidol epoxide to the corresponding homoallylic alcohol introduced the C-7 chiral center. A cross-metathesis reaction was used to create the C5–C4 *E* double bond. The Still–Gennari reaction introduced the 2*Z*,4*E*-diene moiety and finally the Wittig reaction with a propargylic triphenylphosphorane introduced directly the 1,3-enyne unit in a highly efficient stereoselective fashion.

Key words: macrolactin A, cross-metathesis, Still–Gennari reaction, Wittig olefination, dienes

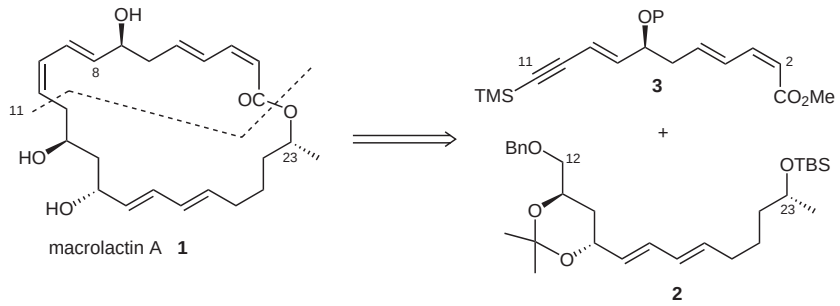
Macrolactin A (**1**), a 24-membered polyene macrolide, isolated in 1989 by Fenical and co-workers from a deep-sea bacterium of unclassified taxonomy along the coast of California,[1] belongs to the class of macrolactins whose other members have been more recently isolated.[2] Macrolactin A displays strong cytotoxic activity in vitro on B16-F10 murine melanoma cells (IC_{50} = 3.5 μg/mL) as well as powerful antiviral activity against *Herpes simplex* types I and II and against human HIV-1 virus replication.[1] Its complex structure and potent antiviral action, combined with an extremely low natural supply, has provided the impetus for a number of synthetic efforts.[3,4] In many of the synthetic approaches, a step-by-step addition of suitable synthons was applied to build up the stereogenic centers and the diene units.[3,4] Our retrosynthetic disconnection of macrolactin A into its upper and lower parts, fragments **3** and **2**, is shown in Scheme 1. We have recently reported an efficient synthesis of the C12–C24 subunit **2**.[5]

In our strategy, the prepared fragment **2** will be assembled with the upper C1–C11 fragment **3**, through alkylation (C11–C12 bond formation) and macrolactonization reactions, followed by the final reduction of the triple bond to the *Z* olefin on C10–C11.

In our first projected route we planned to synthesize segment **3** from precursor **4**, a compound containing two 1,3-enynes. With the novel propargylic benzothiazolyl (BT)-sulfone **6**[6] in hand, we decided to investigate the one-pot Julia olefination[7] in the construction of *trans* double bonds.[8] This approach has never been used in the construction of the C1–C11 segment of macrolactin A (Scheme 2).

As shown in Scheme 3, ring-opening of the known (*R*)-*p*-methoxybenzyl glycidyl ether (**5**) with methyl phenyl sulfone in THF afforded the γ-hydroxy sulfone **8** in 60% yield. Thus, protection as its cyclic acetal led to **9** in 70% yield. The subsequent classical Julia reaction with propargylic aldehyde **7**, prepared from the corresponding alcohol **11**, did not furnish the corresponding β-hydroxy sulfone but only many by-products. A similar trend was also observed in the Julia olefination when sulfone **10**, prepared by derivatization of compound **8**, was used.

As this approach was unsuccessful, we planned to change the two partners of the Julia olefination and we decided to use propargylic BT-sulfone **6**[6] and aldehyde **14** (Scheme 3).



Scheme 1 Retrosynthetic approach to the total synthesis of macrolactin A.

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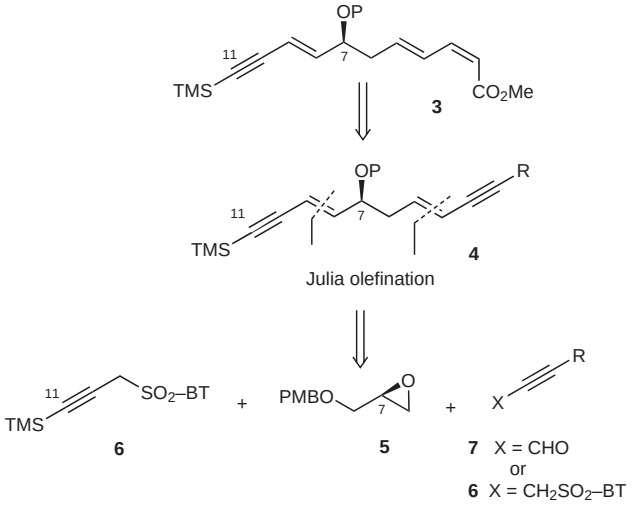
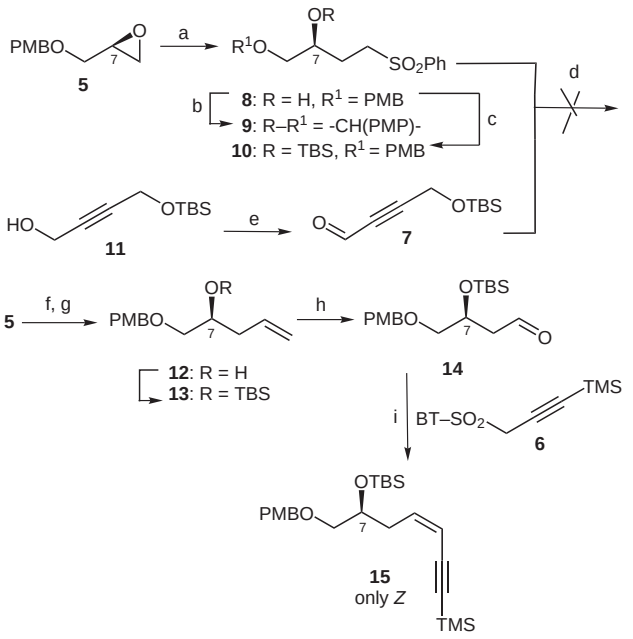


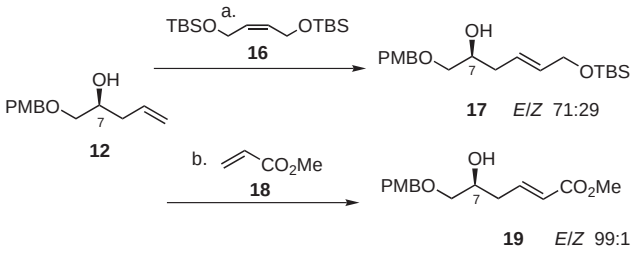
Scheme 2 First proposed route to the C1–C11 fragment.



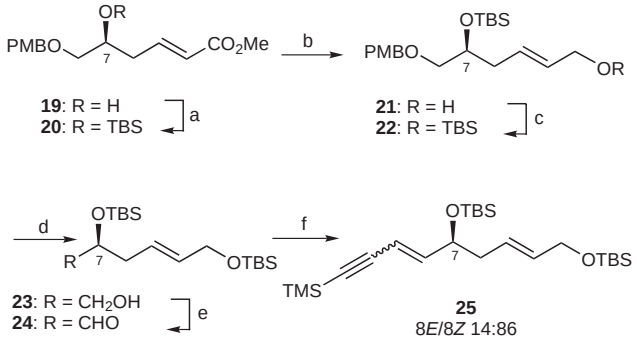
Scheme 3 *Reagents and conditions*: a) $PhSO_2Me$, *n*-BuLi, HMPA, THF, –65 °C to r.t., 30 min (60%); b) DDQ, MS, CH_2Cl_2, r.t., 5 h (70%); c) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 30 min (63%); d) *n*-BuLi, THF, –78 °C to r.t., 20 h; e) Dess–Martin periodinane, CH_2Cl_2, r.t., 20 min (88%); f) vinylMgBr, CuI, THF, –20 °C, 10 min (quant); g) TBSCl, imidazole, DMF, r.t., 16 h (88%); h) OsO_4, NMO, $NaIO_4$, THF, H_2O, r.t., 2 h (quant); i) KHMDS, **6**, THF, –65 °C to r.t., 4 h (56%).

Nucleophilic opening of epoxide **5** with vinylmagnesiumbromide/CuI,[9] and protection of the resulting homoallylic alcohol **12**, led to **13** in high yield (88% yield). The exposure of **13** to OsO_4 and $NaIO_4$ resulted in the formation of aldehyde **14** in quantitative yield. The latter compound was then allowed to react with **6** according to the one-pot Julia protocol, affording **15** in fair yield (56%), but with very high *Z* selectivity.

Since the failure of the previous approaches, a more suitable strategy was planned, as described in Scheme 4. Homoallylic alcohol **12** (Scheme 4), was therefore subjected to a cross-metathesis reaction[10] with alkene **16** and, alternatively, with commercially available methyl acrylate **18**. While ester **19** was obtained with 87% yield and high stereoisomeric ratio (*E*/*Z*, 99:1), olefin **17** was obtained in 50% yield and lower *trans* selectivity (*E*/*Z*, 71:29). Thus, compound **19** represented the advanced fragment for the preparation of **3**.



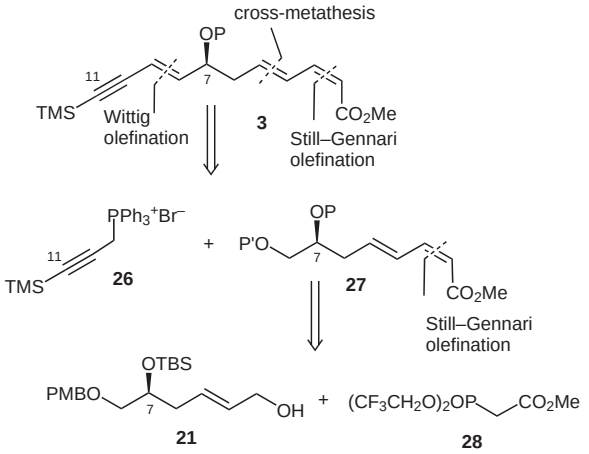
Scheme 4 *Reagents and conditions*: a) **16**, Grubbs II cat. (10 mol%), CH_2Cl_2, reflux, 1 h, 50%; b) **18**, Grubbs II cat. (1 mol%), CH_2Cl_2, reflux, 3 h, 87%.



Scheme 5 *Reagents and conditions*: a) TBSCl, imidazole, CH_2Cl_2, r.t., 20 h (92%); b) DIBAL-H, toluene, 0 °C, 4 h (85%); c) TBSCl, imidazole, CH_2Cl_2, r.t., 24 h (quant.); d) DDQ, pH buffer 7, CH_2Cl_2, 0 °C to r.t., 6 h, 73%; e) Dess–Martin periodinane, CH_2Cl_2, r.t., 3 h (75%); f) **6**, KHMDS, –67 to 0 °C to r.t., 4 h (76%).

Therefore, ester **20**, obtained after silylation of **19** (92% yield), was conveniently converted into the protected triol **22** by reduction to the corresponding alcohol **21** (DIBAL-H, 85% yield) and quantitative protection of the hydroxyl group with TBSCl. Subsequently, compound **22** was selectively deprotected with DDQ (73% yield) affording alcohol **23**, which was oxidized with Dess–Martin periodinane to furnish the desired aldehyde **24** in 75% yield. The latter aldehyde was finally reacted with sulfone **6** via Julia olefination, affording compound **25** in good yield (76%) but still with high *Z* selectivity (*E*/*Z*, 14:86).[11]

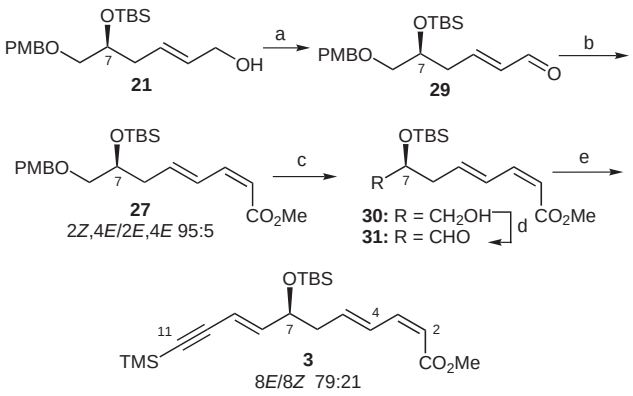
Because of the failure of this route to introduce the correct olefin stereochemistry, a second strategy for the synthesis of the C1–C11 segment was planned as shown in the retrosynthetic Scheme 6. In order to establish the appropriate double bond geometry in a simple short sequence, Still–Gennari[12] and final Wittig olefination were chosen,



Scheme 6 Second proposed route to the C1–C11 fragment.

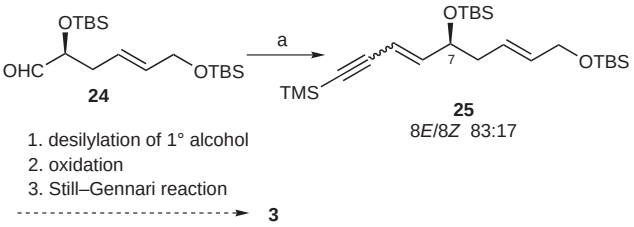
starting from commercially available propargylic triphenylphosphorane **26**, phosphonate **28**, and from alcohol **21** prepared, as described in Schemes 4 and 5, via the cross-metathesis route.

Aldehyde **29** (Scheme 7), easily prepared from alcohol **21** via oxidation with Dess–Martin periodinane, was allowed to react with phosphonate **28** affording (2*Z*,4*E*)-diene **27** with excellent stereoselectivity (*Z*,*E*/*E*,*E*, 95:5) in 70% yield. Deprotection of **27** with DDQ afforded alcohol **30** in 73% yield, which was subsequently oxidized with Dess–Martin periodinane to aldehyde **31** in 75% yield. Preparation of the required compound **3** was finally achieved by reacting the propargylic triphenylphosphorane **26**[13] with aldehyde **31** in the presence of *n*-BuLi at –78 °C. This final Wittig reaction produced the target C1–C11 fragment **3**[14] of macrolactin A in 75% yield and with a good level of stereoselectivity (*E*/*Z*, 79:21 ratio) at the C8–C9 double bond.



Scheme 7 *Reagents and conditions*: a) Dess–Martin periodinane, CH_2Cl_2, r.t., 3 h (78%); b) **28**, KHMDS, 18-crown-6, THF, –78 °C, 4 h (70%); c) DDQ, buffer pH 7, CH_2Cl_2, r.t., 5 h, 73%; d) Dess–Martin periodinane, CH_2Cl_2, r.t., 6 h (75%); e) **26**, *n*-BuLi, –78 °C to 0 °C, 3 h (75%).

In order to improve the selectivity of the Wittig reaction additional experiments were performed. The aldehyde **24** (Scheme 8), prepared according to the conditions reported in Scheme 5, was subjected to the Wittig olefination with phosphorane **26**. Compound **25** was obtained in 74% yield and with 83:17 *E*/*Z* ratio. Considering that there were not substantial improvements in the yield and selectivity in the latter reaction, the shorter route to compound **3** remained that reported in Scheme 7.



Scheme 8 *Reagents and conditions*: a) **26**, *n*-BuLi, –78 °C to 0 °C, 3 h (74%).

In conclusion, after various attempts, an efficient preparation of a key C1–C11 intermediate toward the total synthesis of macrolactin A (**1**) was described showing high stereoselectivity in the introduction of the required three double bonds.

Acknowledgment

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(8) The stereochemical outcome of the one-pot Julia olefination is generally substrate (sulfone and aldehyde) controlled. Moreover, there are some examples where β,γ-unsaturated BT-sulfones give high levels of *E* stereoselectivity (see ref. 7a).

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(13) Attempts were made to prepare the tributyl propargylic phosphorane but we had some problems obtaining it pure.

(14) Compound **3***: R_f* 0.26 (PE–Et_2O–CH_2Cl_2, 99:2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40 (dd, $J_{4,5}$ = 14.4 Hz, $J_{4,3}$ = 11.9 Hz, 1 H), 6.55 (t, $J_{3,2}$ = $J_{3,4}$ = 11.0 Hz, 1 H), 6.18 (dd, $J_{8,9}$ = 16.0 Hz, $J_{8,7}$ = 5.0 Hz, 1 H), 6.03 (dt, $J_{5,4}$ = 15.5 Hz, $J_{5,6}$ = 8.0 Hz, 1 H), 5.72 (d, $J_{9,8}$ = 16.0 Hz, 1 H), 5.61 (d, $J_{2,3}$ = 11.5 Hz, 1 H), 4.26 (m, 1 H), 3.73 (s, 3 H), 2.41 (m, 2 H), 0.89 (s, 9 H), 0.19 (s, 9 H), 0.03 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 146.4, 145.0, 140.4, 129.2, 115.8, 109.2, 103.3, 95.0, 71.8, 51.1, 41.3, 25.8, 18.1, –0.1, –4.6, –4.9. EI-MS: *m*/*z* (%) = 392 (100), 267 (100), 73 (50), 75 (20), 45. Anal. Calcd for $C_{21}H_{36}O_3Si_2$: C, 64.23; H, 9.24. Found: C, 64.32; H, 9.18.