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Stereoselective Synthesis of the C1−C11 and C12−C34 Fragments of Mycalolide A

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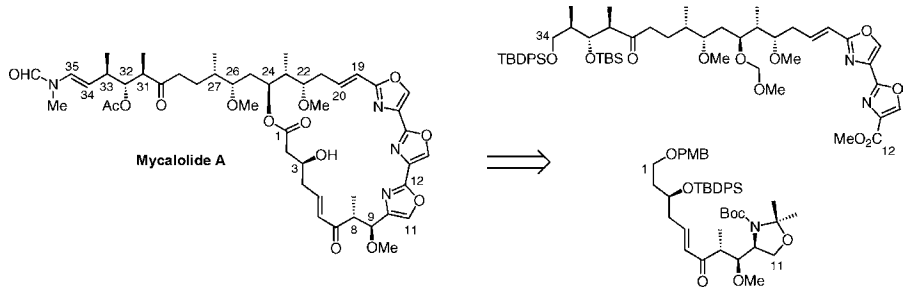
ABSTRACT



A convergent synthesis of the C1−C11 and C12−C34 fragments of mycalolide A is described. Synthetic highlights include a highly *E*-selective cross-metathesis between a vinyl-functionalized bis-oxazole unit and a polypropionate side chain to introduce the C19−C20 double bond and an enzymatic desymmetrization of a *meso*-diol in addition to five stereoselective allylations/crotylations to control the 11 stereogenic centers present in the natural product.

In 1989, Fusetani et al. reported the isolation of mycalolide A (Scheme 1), a secondary metabolite produced by a sponge of the genus *Mycale* sp. collected in the Gokasho Bay of the Kii Peninsula in Japan.[1] This secondary metabolite exhibited antifungal activity against a variety of pathogenic fungi as well as a strong activity against B-16 melanoma cells with IC_{50} values ranging from 0.5 to 1.0 ng/mL (Scheme 1). In addition, it was shown to selectively inhibit the actomyosin Mg^{2+}-ATPase suggesting that it acts as an actin-depolymerization agent.[2]

From a structural perspective, mycalolide A constitutes one of the first known members of a vast family of marine macrolides containing a unique tris-oxazole unit which includes the ulapualides,[3] the jaspisamides,[4] the halishigamides,[5] the kabiramides,[6] and the halichondramides.[7] Its structure, which was elucidated through a combination of chemical degradation, extensive ^{1}H and ^{13}C NMR analysis, and structural correlation experiments,[8] consists of a 25-membered macrolide attached to a highly functionalized aliphatic polyketide side chain bearing eight of the 11 stereogenic centers present in the natural product.

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(1) Fusetani, N.; Yasumuro, K.; Matsunuga, S.; Hashimoto, K. *Tetrahedron Lett.* **1989**, *30*, 2809–2812.

(2) Hori, M.; Saito, S.; Shin, Y.; Ozaki, H.; Fusetani, N.; Karaki, H. *FEBS Lett.* **1993**, *322*, 151–154.

(3) Roesner, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846–847.

(4) Kobayashi, J.; Murata, O.; Shigemori, H. *J. Nat. Prod.* **1993**, *56*, 787–791.

(5) Kobayashi, J.; Tsuda, M.; Fuse, H.; Sasaki, T.; Mikami, Y. *J. Nat. Prod.* **1997**, *60*, 150–154.

(6) (a) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M. *J. Am. Chem. Soc.* **1986**, *108*, 847–849. (b) Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koseki, K.; Noma, M.; Noguchi, H.; Sankawa, U. *J. Org. Chem.* **1989**, *54*, 1360–1363.

(7) Kernan, M. R.; Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 5014–5020.

(8) Matsunaga, S.; Liu, P.; Celatka, C. A.; Panek, J. S.; Fusetani, N. *J. Am. Chem. Soc.* **1999**, *121*, 5605–5606.

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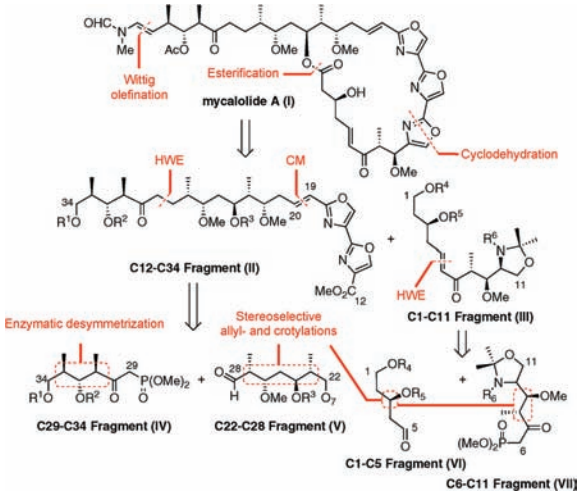
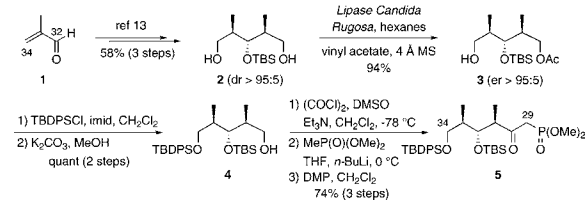
Scheme 1. Retrosynthesis of mycalolide A.



Scheme 2. Synthesis of the C29−C34 β-Ketophosphonate **5**



The promising biological properties displayed by mycalolide A in conjunction with its challenging structure and the fact that only one total synthesis has been reported so far[9,10] prompted us to initiate studies toward its total synthesis. We describe here the results of our endeavor.

Our strategy for the synthesis of mycalolide A relied on four key disconnections: an unusual cross-metathesis (CM) between a vinyl-functionalized bis-oxazole unit and the C20−C34 polypropionate fragment bearing a terminal olefin, an esterification to link the C12−C34 fragment **II** and the C1−C11 fragment **III**, a Robinson−Gabriel-type cyclodehydration to form the third oxazole ring and concomitantly generate the macrolide, and a Wittig olefination using an *N*-methylformamide phosphonium salt to install the enamide moiety and complete the synthesis of the natural product (Scheme 1).

Our first instinct when trying to devise a straightforward strategy to access mycalolide A was to apply a CM between a vinyl-functionalized mono-, bis-, or tris-oxazole unit and a terminal olefin. Interestingly, however, despite the plethora of examples which have been reported in the literature in the field of CM within the last couple of decades,[11] there has only been a few examples involving vinyl-functionalized azoles.[10s,12] In this context, and with the scope to validate this strategy, we embarked on the synthesis of the two CM coupling partners.

The preparation of the C20−C34 fragment of mycalolide A relied on a Horner−Wadsworth−Emmons (HWE) reaction between a C29−C34 β-ketophosphonate of type **IV** and a C22−C28 aldehyde of type **V**. The synthesis of the former began by the preparation of *meso*-diol **2** which was obtained in three steps and 58% overall yield starting from methacrolein (**1**) and following a reported procedure (Scheme 2).[13] The resulting *meso*-diene was then subjected to a diastereoselective double hydroboration (9-BBN, THF, −85 °C) which, upon oxidation, delivered the *meso*-diol **2** in 70% yield (dr >95:5). Desymmetrization of the latter through a lipase-mediated acetylation (*Candida rugosa*, vinyl acetate, hexane, 4 Å MS, 36 h)[14] afforded the corresponding monoacetate **3** in 97% yield as a single stereoisomer (er >95:5).[15] Protection of the remaining primary alcohol as a *tert*-butyldiphenylsilyl ether (TBDPSCl, imidazole, CH_2Cl_2) and saponification of the acetate group (K_2CO_3, MeOH) led to alcohol **4** which was eventually oxidized under Swern conditions to provide the corresponding aldehyde. The aldehyde was then treated with a THF solution of $LiCH_2P(O)(OMe)_2$ (prepared in situ from methyl dimethyl phosphonate, *n*-BuLi, THF, 0 °C)[16] to afford the β-hydroxyphosphonate intermediate. The latter was ultimately oxidized to the corresponding β-ketophos-

(9) (a) Liu, P.; Panek, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 1235–1236. (b) Panek, J. S.; Liu, P. *J. Am. Chem. Soc.* **2000**, *122*, 11090–11097.

(10) For earlier synthetic studies on mycalolide A and related tris-oxazoles, see: (a) Knight, D. W.; Pattenden, G.; Rippon, D. E. *Synlett* **1990**, 36–37. (b) Kiefel, M. J.; Maddock, J.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 3227–3230. (c) Pattenden, G. *J. Heterocycl. Chem.* **1992**, *29*, 607–618. (d) Yoo, S.-K. *Tetrahedron Lett.* **1992**, *33*, 2159–2162. (e) Chattopadhyay, S. K.; Pattenden, G. *Tetrahedron Lett.* **1995**, *36*, 5271–5274. (f) Panek, J. S.; Beresis, R. T.; Celatka, C. A. *J. Org. Chem.* **1996**, *61*, 6494–6495. (g) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1996**, *61*, 6496–6497. (h) Liu, P.; Celatka, C. A.; Panek, J. S. *Tetrahedron Lett.* **1997**, *38*, 5445–5448. (i) Celatka, C. A.; Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1997**, *38*, 5449–5452. (j) Chattopadhyay, S. K.; Pattenden, G. *Synlett* **1997**, 1342–1344. (k) Chattopadhyay, S. K.; Pattenden, G. *Synlett* **1997**, 1345–1348. (l) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6143–6146. (m) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6147–6150. (n) Kempson, J.; Pattenden, G. *Synlett* **1999**, 533–536. (o) Chattopadhyay, S. K.; Kempson, J.; McNeil, J.; Pattenden, G.; Reader, M.; Rippon, D. E.; White, D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2415–2428. (p) Pattenden, G.; Chattopadhyay, S. K. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 2429–2454. (q) Panek, J. S.; Celatka, C. A. *Tetrahedron Lett.* **2002**, *43*, 7043–7046. (r) Suenaga, K.; Kimura, T.; Kuroda, T.; Matsui, K.; Miya, S.; Kuribayashi, S.; Sakakura, A.; Kigoshi, H. *Tetrahedron* **2006**, *62*, 8278–8290. (s) Kimura, T.; Kuribayashi, S.; Sengoku, T.; Matsui, K.; Ueda, S.; Hayakawa, I.; Suenaga, K.; Kigoshi, H. *Chem. Lett.* **2007**, *36*, 1490–1491. (t) Pattenden, G.; Ashweek, N. J.; Baker-Glenn, C. A. G.; Walker, G. M.; Yee, J. G. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4359–4363.

(11) (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923. (b) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8–23. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

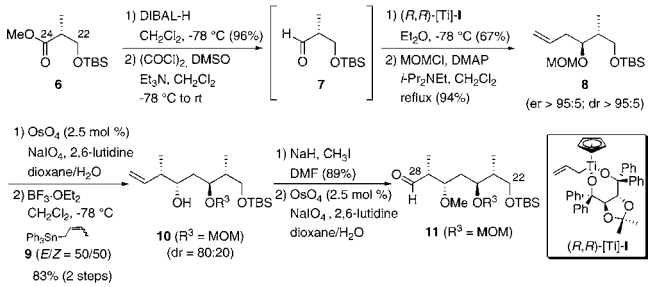
(12) For examples of CM involving vinyl-functionalized oxazoles, see: (a) Hoffman, T. J.; Rigby, J. H.; Arseniyadis, S.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 2400–2403. For examples of CM involving vinyl-functionalized thiazoles, see: (b) Dash, J.; Arseniyadis, S.; Cossy, J. *Adv. Synth. Catal.* **2007**, *349*, 152–156. For applications in natural product synthesis, see: (c) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Org. Lett.* **2007**, *9*, 3425–3427. (d) Gebauer, J.; Arseniyadis, S.; Cossy, J. *Eur. J. Org. Chem.* **2008**, 2701–2704.

(13) (a) Harada, T.; Matsuda, Y.; Wada, I.; Uchimura, J.; Oku, A. *Chem. Commun.* **1990**, 21–22. (b) Harada, T.; Matsuda, Y.; Wada, I.; Uchimura, J.; Oku, A. *J. Am. Chem. Soc.* **1993**, *115*, 7665–7674.

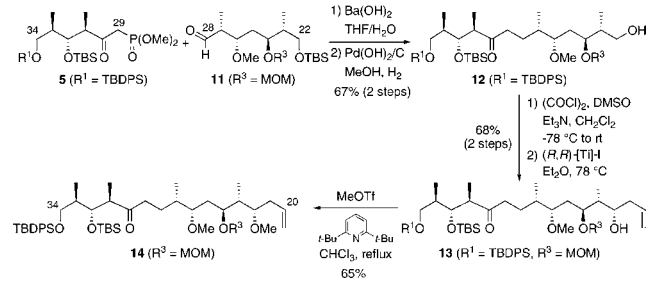
(14) (a) Chênevert, R.; Courchesne, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2093–2096. (b) Chênevert, R.; Courchesne, G.; Caron, D. *Tetrahedron: Asymmetry* **2003**, *14*, 2567–2571. (c) Kann, N.; Rein, T. J. *J. Org. Chem.* **1993**, *58*, 3802–3804, and refences cited therein.

(15) The enantiomeric excess of **13** was measured by ^{1}H NMR of the corresponding mandelic ester, while the assignment of the absolute configuration was made by comparison with the $[\alpha]_D$ reported in the literature for the known compound ($[\alpha]^{20}_D$ −8.2, *c* 2.36, $CHCl_3$);^{exp} ($[\alpha]^{20}_D$ −8.6, *c* 2.37, $CHCl_3$)^{lit}.

Scheme 3. Synthesis of the C22−C28 Aldehyde **11**



Scheme 4. Synthesis of the CM Coupling Partner **14**



phonate **5** thus completing the synthesis of the C29−C34 subunit in nine steps and 40.3% overall yield starting from methacrolein **1** (Scheme 2).

The construction of the C22−C28 aldehyde subunit commenced from commercially available (*R*)-Roche ester and proceeded through an initial three-step sequence which included the protection of the primary alcohol as a TBS ether **6**, the reduction of the ester moiety, and the oxidation of the resulting alcohol to the corresponding aldehyde (Scheme 3). The latter was then subjected to a diastereoselective allylation using the (*R*,*R*)-[Ti]-**I** complex (THF, −78 °C)[17] to afford the corresponding homoallylic alcohol (64.3% yield from **6**, dr >95:5, er >95:5)[18,19] which was subsequently protected as a methoxymethyl ether (MOMCl, DMAP, *i*-PrNEt$_2$, CH_2Cl_2, reflux, 94% yield). Olefin **8** was then engaged in an OsO_4-catalyzed oxidative cleavage (OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/H_2O),[20] and the resulting aldehyde was treated with (*E*/*Z*)-triphenyl crotylstannane **9**[21] under Keck's conditions[22] (BF_3•OEt_2, CH_2Cl_2, −78 °C) to effect a substrate-controlled diastereoselective crotylstannylation (83%, dr 80:20).[19,23,24] The resulting alcohol **10** was then converted to a methoxy ether (**(**CH_3I, NaH, DMF, 89% yield) and the terminal olefin subjected to an OsO_4-catalyzed oxidative cleavage, thus completing the synthesis of the C22−C28 aldehyde subunit **11** in nine steps and 45.7% overall yield starting from the (*R*)-Roche ester.

With the two fragments **5** and **11** in hand, the stage was set for the key HWE olefination which would afford the C22−C34 polypropionate fragment of mycalolide A (Scheme 4). Hence, *β*-ketophosphonate **5** was treated with $Ba(OH)_2$•$8H_2O$[25] in wet THF (THF/H_2O = 40:1) followed by aldehyde **11** to provide the coupled product as a single (*E*)-isomer in 80% yield (Scheme 4). Reduction of the enone to the corresponding ketone using $Pd(OH)_2$/C in MeOH under a hydrogen atmosphere occurred with concomitant cleavage of the C22 primary TBS ether[26] thus affording alcohol **12** in 85% yield. Swern oxidation to the corresponding aldehyde and treatment with the (*R*,*R*)-[Ti]-**I** complex (Et_2O, −78 °C) installed the (22*S*) stereogenic center and provided homoallylic alcohol **13** as a single stereoisomer in 68% yield over two steps (dr >95:5).[27] As an attempt to methylate the C22 hydroxyl group using NaH/MeI had caused epimerization at C31, milder conditions were applied. To our delight, exposure of **13** to MeOTf and 2,6-di-*tert*-butylpyridine in refluxing $CHCl_3$ produced the desired methylated product **14** as a single stereoisomer in 65% yield (93% based on recovered starting material). The preparation of the C20−C34 polyketide fragment of mycalolide A was thus achieved in 14 steps and 13.2% overall yield starting from methacrolein **1**.

With the C20−C34 fragment secured, we next turned our attention toward the synthesis of the vinyl-functionalized bisoxazole subunit which would be engaged in the key CM (Scheme 5). Hence, treatment of acrylamide **15** and ethyl bromopyruvate **16** with $NaHCO_3$ (THF, 55 °C) followed by TFAA (THF, 0 °C) and saponification of the resulting ester using LiOH•H_2O in a THF/H_2O mixture afforded carboxylic acid **17** in 72% yield over three steps. The latter was then coupled with (±)-serine methyl ester hydrochloride using standard conditions (EDC, HOBt, NMM, CH_2Cl_2)[28] to afford *β*-hydroxy amide **18** (72% yield) which in turn was engaged

(16) (a) Heathcock, C. H.; Hadley, C. R.; Rosen, T.; Theisen, P. D.; Hecker, S. J. *J. Med. Chem.* **1987**, *30*, 1858–1863. (b) Yasuda, N.; Hsiao, Y.; Jensen, M. S.; Rivera, N. R.; Yang, C.; Wells, K. M.; Yau, J.; Palucki, M.; Tan, L.; Dormer, P. G.; Volante, R. P.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2004**, *69*, 1959–1966.

(17) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. J. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. (b) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807–832.

(18) The diastereomeric ratio was determined by crude ^{1}H NMR analysis, and the absolute configuration of the C24 stereogenic center was determined as (24*S*) by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-mandelic esters.

(19) Seco, J. M.; Quinoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925.

(20) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

(21) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schrieber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583–5601.

(22) (a) Yamamoto, Y. *Aldrichimica Acta* **1987**, *20*, 45–49. (b) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243–249. (c) Keck, G. E.; Savin, K. A.; Creesman, E. N. K.; Abbot, D. E. *J. Org. Chem.* **1994**, *59*, 7889–7896. (d) Keck, G. E.; Savin, K. A.; Weglarz, M. A.; Cressman, E. N. K. *Tetrahedron Lett.* **1996**, *37*, 3291–3294.

(23) The absolute configuration of the C26 stereogenic center was determined as (26*S*) by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-mandelic esters.

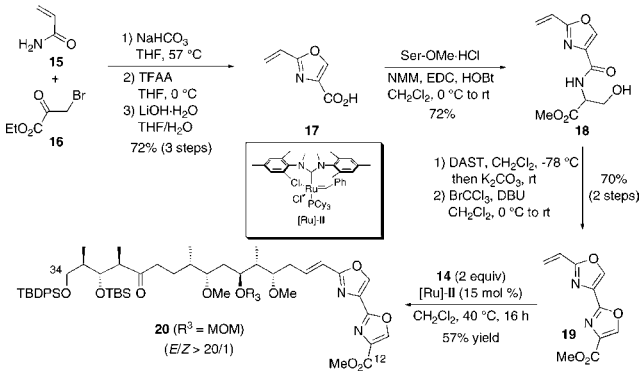
(24) (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **1984**, *23*, 556–559. (b) Reetz, M. T.; Kessler, K.; Jung, M. *Tetrahedron* **1984**, *40*, 4327–4336. (c) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881–5884. Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462–468.

(25) (a) Alvarez-Ibarra, C.; Arias, S.; Bañón, G.; Fernández, M.; Rodriguez, V.; Sinisterra, J. *Chem. Soc. Chem. Commun.* **1987**, 1509–1511. (b) Paterson, I.; Yeung, K. S.; Smaill, J. B. *Synlett* **1993**, 774–776.

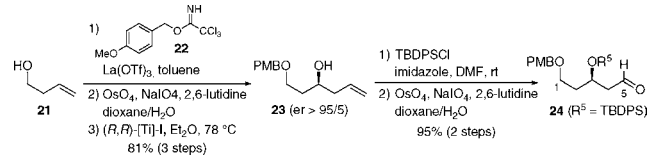
(26) For a review on selective monodeprotection of bis-silyl ethers, see: Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833–5871. For the use of hydrogenation conditions in silyl ether deprotection, see: (a) Toshima, K.; Yanagawa, K.; Mukaiyama, S.; Tatsuta, K. *Tetrahedron Lett.* **1990**, *31*, 6697–6698. (b) Lee, K.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 7808–7812. (c) Rotulo-Sims, D.; Prunet, J. *Org. Lett.* **2004**, *4*, 4701–4704.

(27) The absolute configuration of the C22 stereogenic center was determined as (22*S*) by ^{1}H NMR analysis of the corresponding (*R*)- and (*S*)-mandelic esters.

Scheme 5. Synthesis of the C12−C34 Fragment **20**



Scheme 6. Synthesis of the C1−C5 Fragment **24**

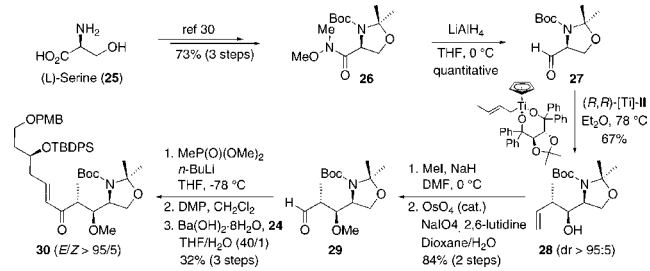


in a sequential DAST-mediated cyclodehydration (CH_2Cl_2, −78 °C)/dehydrobromination ($BrCCl_3$, DBU, CH_2Cl_2, 0 °C) that led to the desired bisoxazole **19** in 70% yield over two steps. The C20−C34 polyketide fragment **14** and bisoxazole **19** were then coupled using Grubbs second-generation catalyst, [Ru]-**II** (CH_2Cl_2, 40 °C, 16 h), to afford the C12−C34 fragment of mycalolide A **20** in a moderate 57% yield and an excellent *E*-stereoselectivity (*E*/*Z* > 20:1).

The synthesis of the C1−C11 fragment of mycalolide A relied on a HWE between a C1−C5 aldehyde of type **VI** and a C6−C11 β-ketophosphonate of type **VII**. The former was prepared starting from 3-buten-1-ol (**21**) (Scheme 6). Hence, **21** was first converted into the corresponding *para*-methoxybenzyl ether using trichloroacetimidate **22** in the presence of a catalytic amount of $La(OTf)_3$ (toluene, rt, 95% yield). An OsO_4-catalyzed oxidative cleavage then afforded the corresponding aldehyde[19] which was subsequently treated with the (*R*,*R*)-[Ti]-**II** complex to provide homoallylic alcohol **23** in 85% yield over two steps (er >95:5).[29] The latter was then protected as a TBS ether, and the terminal olefin was finally oxidatively cleaved to unveil the desired aldehyde **24** in 95% yield over two steps.

The synthesis of the C6−C11 β-ketophosphonate, on the other hand, began with the preparation of the Weinreb amid **26** starting from (L)-serine **25** according to a reported procedure[30] (73% over three steps) (Scheme 7). Weinreb amide **26** was then reduced to the corresponding aldehyde **27** using $LiAlH_4$ (THF, 0 °C, quantitative) and immediately engaged in a diastereoselective crotyltitanation using the (*R*,*R*)-[Ti]-**II** complex (Et_2O, −78 °C) to afford the corresponding homoallylic alcohol **28** in decent yield and excellent selectivity (67% yield, dr >95:5). Methyl ether formation (MeI, NaH, DMF, 0 °C) followed by OsO_4-catalyzed oxidative cleavage of the terminal olefin then furnished aldehyde **29** in 84% yield over two steps. Immediate treatment with $LiCH_2P(O)(OMe)_2$ ($MeP(O)(OMe)_2$, *n*-BuLi, THF, 0 °C) followed by a Dess−Martin periodinane (DMP)-mediated oxidation of the resulting β-hydroxyphosphonate then supplied the desired β-ketophosphonate in 46% yield. A $Ba(OH)_2$-mediated HWE olefination between the C1−C5 aldehyde and the C6−C11 β-ketophosphonate finally afforded the desired C1−C11 fragment of mycalolide A, compound **30**, in 69% yield (*E*/*Z* > 95:5). This sequence was thus carried out in 10 steps and 13.1% overall yield starting from (L)-serine **25**.

Scheme 7. Synthesis of the C1−C11 Fragment **30**



In conclusion, we have completed the synthesis of the C1−C11 and C12−C34 fragments of mycalolide A. The synthesis includes a highly *E*-selective cross-metathesis between a vinyl-functionalized bis-oxazole unit and a polypropionate side chain to introduce the C19−C20 double bond, an enzymatic desymmetrization of a *meso*-diol to control the three stereogenic centers at C31, C32, and C33, and five stereoselective allylations/crotylations to control the stereogenic centers at C3, C8, C9, C22, C24, C26, and C27. Future efforts will be dedicated in coupling the two fragments together, performing the Robinson−Gabriel-type cyclodehydration to form the macrolide and introducing the enamide moiety through a Wittig olefination to complete the synthesis. These efforts will be reported in due course.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Chattopadhyay, S. K.; Biswas, S.; Pal, B. K. *Synthesis* **2006**, *8*, 1289–1293. For a review of peptide coupling reagents, see: Han, S.-Y.; Kim, Y.-A. *Tetrahedron* **2004**, *60*, 2447–2467.

(29) The enantiomeric ratio and absolute configuration were determined by crude ^1H NMR analysis of the corresponding (*R*)-mandelic ester and confirmed by comparison with the physical data reported in the literature (exp: $[\alpha]^{20}_D$ + 1.5, *c* 1.0, $CHCl_3$); lit: $[\alpha]^{20}_D$ + 1.0, *c* 1.0, $CHCl_3$), see: Smith, A. B., III; Minbiole, K. B.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942–10953.

(30) (a) Ageno, G.; Banfi, L.; Cascio, G.; Guanti, G.; Manghisi, E.; Riva, R.; Roccaa, V. *Tetrahedron* **1995**, *51*, 8121–8134. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.