TOTAL SYNTHESIS OF MYCALAMIDE A. FURTHER SYNTHETIC STUDY OF THE RIGHT HALF

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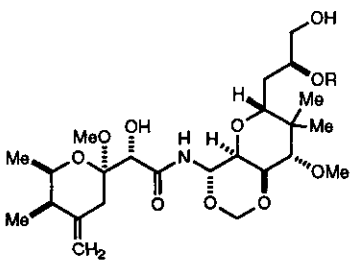
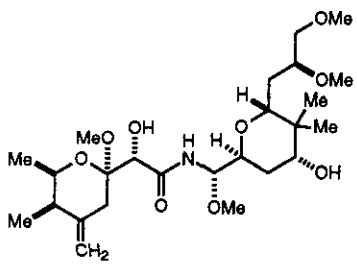
Abstract - The right half **5** of mycalamide A (**1**) was synthesized starting from (*R*)- or (*S*)-pantolactone *via* the Sharpless asymmetric dihydroxylation as the key step. The total synthesis of mycalamide A (**1**) was accomplished by coupling of the right and left halves.

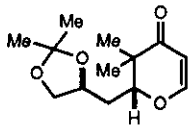
Mycalamides A (**1**) and B (**2**) are potent antiviral and antitumor compounds isolated from the New Zealand marine sponge of the genus *Mycale*.[1] Onnamides and theopederins, structurally related compounds, have also been isolated from the Japanese marine sponge of the genus *Theonella*.[2] The structure of these compounds is strikingly similar to that of pederin (**3**), a strong insect poison isolated from *Paederus fuscipes*.[3] Recently, their unique structure and potent bioactivity have attracted the attention of synthetic organic chemists.[4,5] The first total synthesis of mycalamide A (**1**), B (**2**), and onnamide A was achieved by Hong and Kishi.[4] We have also reported the formal total synthesis of mycalamide A (**1**),[6] in which the right half azide (**5**) was stereoselectively synthesized *via* α,β-unsaturated ketone (**4**) which was synthesized by two routes starting from (*S*)-malic acid



Mycalamide A (**1**) : R=H
Mycalamide B (**2**) : R=Me



Pederin (**3**)



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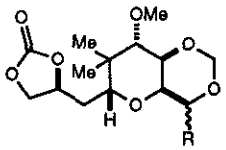
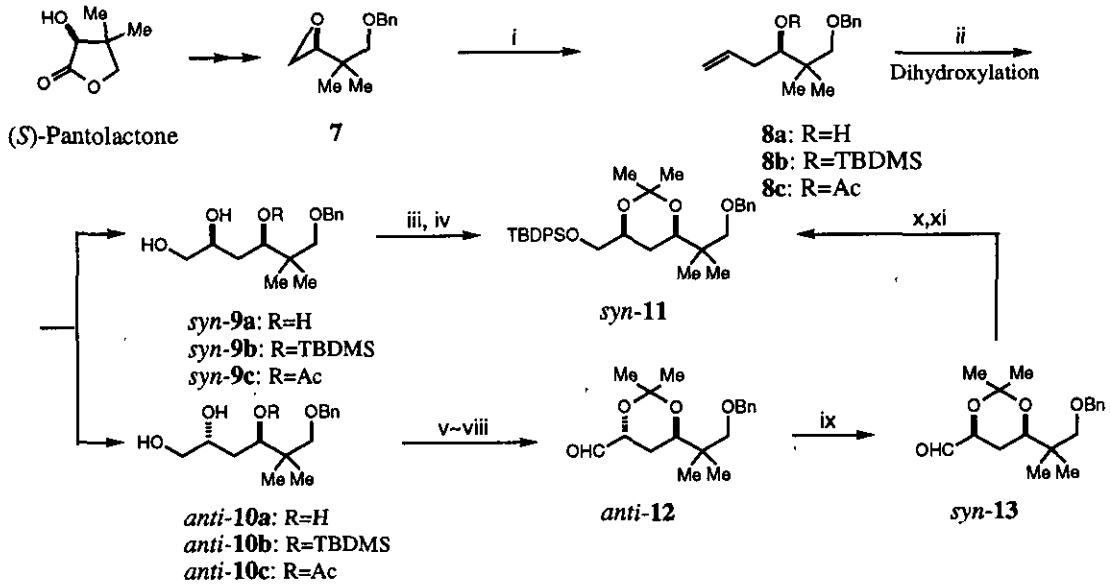


5: R = N_3
6: R = NH_2

and (*R*)- or (*S*)-pantolactone. However, for the large-scale preparation, the alternative, efficient route for the synthesis of **5** was still required. We now report our further study of the synthesis of the right half **5** and the total synthesis of mycalamide A (**1**).

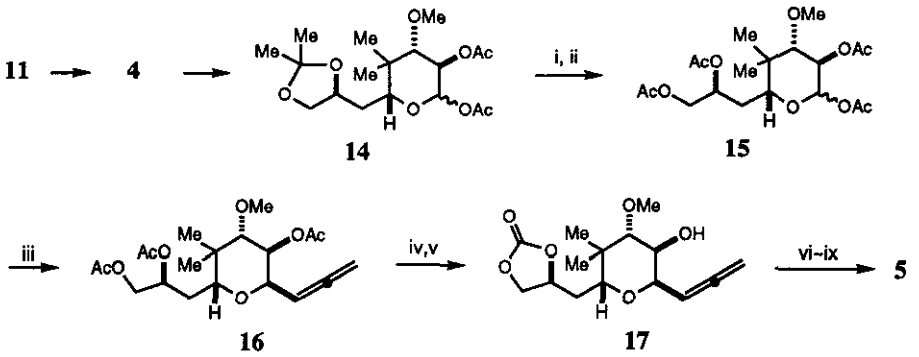
The synthesis of the key intermediate *syn*-**11** leading to **4** was achieved starting from epoxide (**7**)[6] prepared from (*R*)- or (*S*)-pantolactone. The reaction of epoxide (**7**) with vinylmagnesium bromide in the presence of CuI in THF produced allyl alcohol (**8a**) in 89% yield. The dihydroxylation of **8a** with OsO_4 in the presence of *N*-methylmorpholine oxide (NMO) in acetone-*t*-BuOH-H_2O produced a mixture of *syn*-**9a** and *anti*-**10a** (88%) in a ratio of 1:1.17. The same reaction using *t*-butyldimethylsilyl ether (**8b**) and acetate (**8c**) derived from **8a**



Reagents and Conditions: (i) CH_2=CHMgBr, CuI, THF, -20°C~room temperature (89%); (ii) a) OsO_4, NMO (150 mol %), acetone, *t*-BuOH, H_2O, room temperature; b) $(DHQ)_2PHAL$ (1 mol %), OsO_4 (0.2 mol %), $K_3Fe(CN)_6$ (300 mol %), K_2CO_3 (300 mol %), *t*-BuOH, H_2O, 0°C; c) $(DHQD)_2PHAL$ (1 mol %), OsO_4 (0.2 mol %), $K_3Fe(CN)_6$ (300 mol %), K_2CO_3 (300 mol %), *t*-BuOH, H_2O, 0°C; d) $(DHQ)_2PYR$ (1 mol %), OsO_4 (0.2 mol %), $K_3Fe(CN)_6$ (300 mol %), K_2CO_3 (300 mol %), *t*-BuOH, H_2O, 0°C; (iii) *t*-$BuPh_2SiCl$, imidazole, DMF, room temperature; (iv) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, room temperature (92% from **9a**); (v) PivCl, pyridine, CH_2Cl_2, 0°C; (vi) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, room temperature; (vii) K_2CO_3, MeOH, room temperature; (viii) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78°C~room temperature (68% from **10a**); (ix) K_2CO_3, MeOH, room temperature; (x) $NaBH_4$, EtOH, room temperature; (xi) *t*-$BuPh_2SiCl$, imidazole, DMF, room temperature (62% from **12**).

gave a mixture of *syn*-**9b, c** and *anti*-**10b, c** in a ratio of 1.20:1 (90%) and 1:2.44 (68%), respectively. The Sharpless asymmetric dihydroxylation (AD)[7] of **8a,b, c** was then investigated. The AD reaction of **8a** using $(DHQ)_2PHAL$,[8] which was expected to give *syn*-diol (**9a**), proceeded with a slight excess of the desired **9a** in a ratio of 1.27:1 (82%).[9] In the case of silyl ether (**8b**) and acetate (**8c**), the same reaction using $(DHQ)_2PHAL$ proceeded with unexpected *anti*-stereoselection giving *anti*-**10b** and *anti*-**10c** as the major products in a *syn-anti* ratio of 1:2.48 (50%; 99% based on the consumed **8b**) and 1:2.46 (59%), respectively.[9,10] Finally, the AD reaction was carried out using $(DHQ)_2PYR$ which generally gives good results for monosubstituted terminal olefins.[11] The reaction of **8a** using $(DHQ)_2PYR$ yielded the desired *syn*-**9a** as the major product in a ratio of 2.45:1 (90%). The *syn*-**9a** was then transformed to acetonide (**11**) in 92% yield by successive silylation and acetonization. On the other hand, *anti*-**10a** was also converted into the desired *syn*-acetonide (**11**) as follows. After protection of the primary and secondary hydroxyl groups in **10a** as the pivaloyl ester and acetonide, respectively, hydrolysis of the resulting ester followed by Swern oxidation produced the *anti*-aldehyde (**12**) in 68% yield (from **10a**). Epimerization of **12** with K_2CO_3 in MeOH smoothly took place giving isomeric *syn*-aldehyde (**13**), which upon treatment with $NaBH_4$ followed by *t*-butyldiphenylsilyl chloride gave acetonide (**11**) in 62% yield (from **12**). The present route provided the desired *syn*-compound (**11**) in 52% overall yield from the epoxide (**7**) in four steps (63% overall yield including the conversion of *anti*-**10a** to *syn*-**11**).[12]

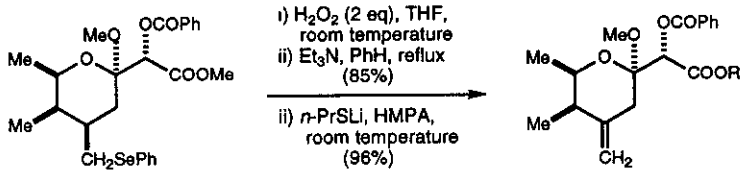
Using the route previously described,[6] the acetonide (**11**) was converted into the diacetate (**14**) *via* the α,β-unsaturated ketone (**4**). The right half azide (**5**) was then synthesized from **14** with a small modification of the previous route,[6] which was more suitable for large-scale preparation and gave better reproducibility.



Reagents and Conditions: (i) AcOH-H_2O (10:1), 60°C, 20min; (ii) Ac_2O, pyridine, room temperature (92% from **14**); (iii) PropargylTMS, TMSOTf, MeCN, 0°C (76%); (iv) K_2CO_3, MeOH, room temperature; (v) Im_2CO,THF, room temperature (91% from **16**); (vi) O_3, CH_2Cl_2, -78°C; Me_2S, -78-0°C; (vii) $(CH_2O)_n$, CSA, CH_2Cl_2, 0°C; (viii) Ac_2O, pyridine, room temperature; (ix) $TMSN_3$, TMSOTf, MeCN, 0°C (57% from **17**).

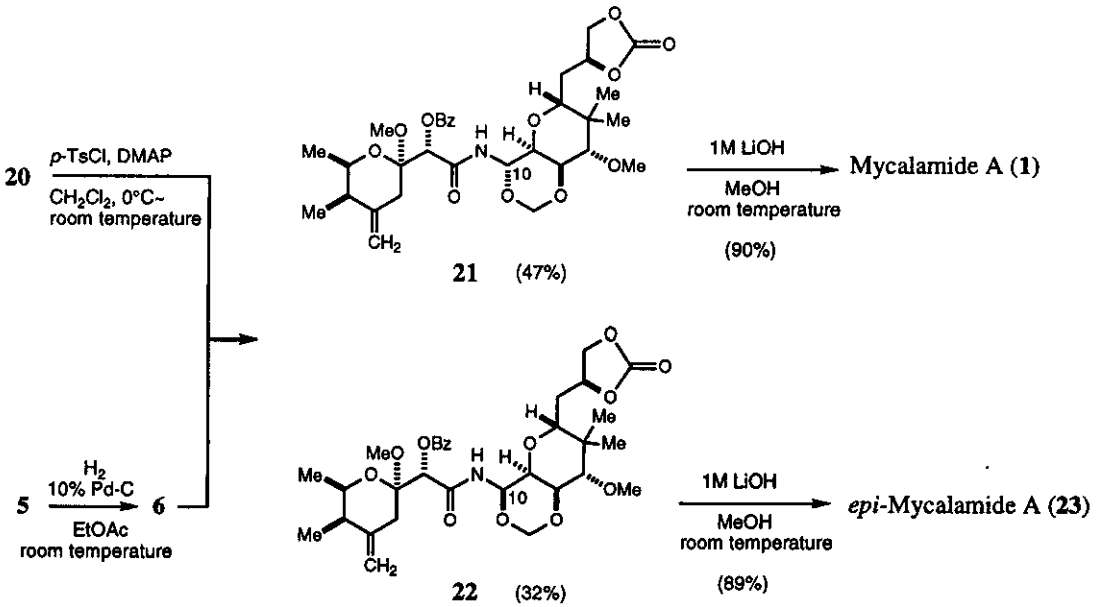
Hydrolysis of the acetonide (**14**) with aq. AcOH followed by acetylation gave the tetraacetate (**15**) in 92% yield. Upon treatment of **15** with propargyltrimethylsilane in the presence of trimethylsilyl triflate (TMSOTf) in MeCN,[4] introduction of the allene group stereoselectively took place producing β-allene (**16**) in 76% yield as a single compound. Treatment of the triacetate (**16**) with K_2CO_3 in MeOH followed by 1,1'-carbonyldiimidazole (Im_2CO) in THF afforded carbonate (**17**) in 91% yield, which was converted into the right half azide (**5**) as an inseparable diastereomers (1:1.1) in 57% yield in four steps; (1) ozonolysis of the allene to aldehyde, (2) treatment with paraformaldehyde, (3) acetylation with Ac_2O, and (4) introduction of azide with $TMSN_3$.

On the other hand, the left half **20** was synthesized in three steps from **18**, which was already synthesized during our total synthesis of pederin (**3**).[13] The ester (**18**) was treated with H_2O_2 in THF followed by Et_3N in refluxing benzene to give the olefin (**19**) in 85% yield, which upon treatment with *n*-PrSLi in HMPA produced the carboxylic acid (**20**) (96 %), corresponding to the left half of **1**.



18 **19:** R=Me **20:** R=H

Having completed the synthesis of the left and right halves, **20** and **5**, we then undertook their coupling under Kishi's conditions.[4] Treatment of the carboxylic acid (**20**) with *p*-TsCl in the presence of 4-dimethyl-



aminopyridine (DMAP) in CH_2Cl_2 followed by addition of amine (**6**), prepared from the azide (**5**) by hydrogenation, produced a mixture of 10α-**21** (47%) and its 10β-epimer **22** (32%). Hydrolysis of **21** and **22** with 1M LiOH in MeOH gave synthetic mycalamide A (**1**) and *epi*-mycalamide A (**23**)[14] in 90 and 89% yield, respectively. The spectral data (^{1}H nmr, ir, $[\alpha]_D$) of the synthetic **1** were identical with those of mycalamide A synthesized by Kishi.[4]

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9. Such a low selectivity or anomaly in the Sharpless asymmetric dihydroxylation was also reported by several groups: (a) ref. 5c; (b) E. M. Carreira and J. Du Bois, *J. Am. Chem. Soc.*, 1994, **116**, 10825; (c) M. Iwashita, T. Kinsho, and A. B. Smith, III, *Tetrahedron Lett.*, 1995, **36**, 2199.

10. Reaction of silyl ether (**8b**) and acetate (**8c**) using $(DHQD)_2PHAL$, which was expected to give the *anti*-compound, also yielded *anti*-**9c** and *anti*-**10c** as the major products in a *syn-anti* ratio of 1:1.82 (60%; 80% based on the consumed **8b**) and 1:5.58 (64%; 89% based on the consumed **8c**), respectively. Thus, both reagents, $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$, gave the *anti*-compounds as major products in this system.[9]

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12. In the former synthesis,[6] the overall yield of **11** from the epoxide (**7**) was 43% in six steps.

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