

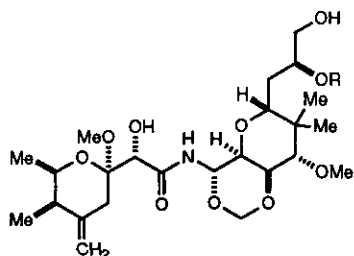
TOTAL SYNTHESIS OF MYCALAMIDE A. FURTHER SYNTHETIC STUDY OF THE RIGHT HALF

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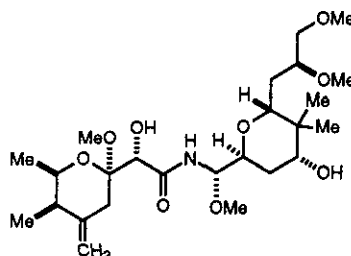
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Abstract - The right half **5** of mycalamide A (**1**) was synthesized starting from (*R*)- or (*S*)-pantolactone *via* the Sharpless asymmetric dihydroxylation as the key step. The total synthesis of mycalamide A (**1**) was accomplished by coupling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

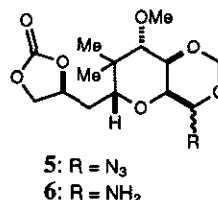
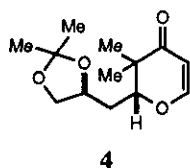
Mycalamides **1** and **2** are potent antiviral and antitumor compounds isolated from the New Zealand marine sponge of the genus *Mycale*.¹ Onnamides and theopederins, structurally related compounds, have also been isolated from the Japanese marine sponge of the genus *Theonella*.² The structure of 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**), **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

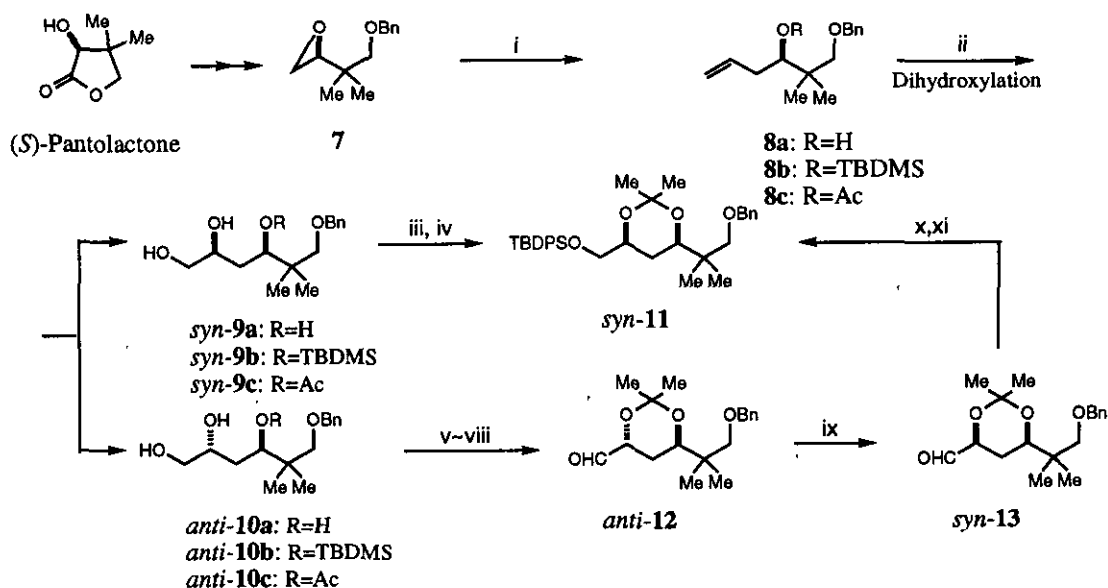


Pederin (**3**)



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**).

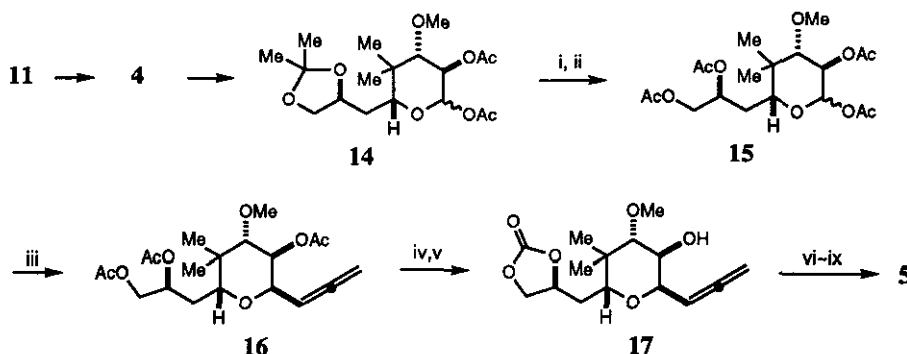
The synthesis of the key intermediate *syn*-**11** leading to **4** was achieved starting from epoxide (**7**)⁶ prepared from (*R*)- or (*S*)-pantolactone. The reaction of epoxide (**7**) with vinylmagnesium bromide in the presence of CuI in THF produced allyl alcohol (**8a**) in 89% yield. The dihydroxylation of **8a** with OsO₄ in the presence of *N*-methylmorpholine oxide (NMO) in acetone-*t*-BuOH-H₂O 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) CH₂=CHMgBr, CuI, THF, -20°C~room temperature (89%); (ii) a) OsO₄, NMO (150 mol %), acetone, *t*-BuOH, H₂O, room temperature; b) (DHQ)₂PHAL (1 mol %), OsO₄ (0.2 mol %), K₃Fe(CN)₆ (300 mol %), K₂CO₃ (300 mol %), *t*-BuOH, H₂O, 0°C; c) (DHQD)₂PHAL (1 mol %), OsO₄ (0.2 mol %), K₃Fe(CN)₆ (300 mol %), K₂CO₃ (300 mol %), *t*-BuOH, H₂O, 0°C; d) (DHQ)₂PYR (1 mol %), OsO₄ (0.2 mol %), K₃Fe(CN)₆ (300 mol %), K₂CO₃ (300 mol %), *t*-BuOH, H₂O, 0°C; (iii) *t*-BuPh₂SiCl, imidazole, DMF, room temperature; (iv) Me₂C(OMe)₂, CSA, CH₂Cl₂, room temperature (92% from **9a**); (v) PivCl, pyridine, CH₂Cl₂, 0°C; (vi) Me₂C(OMe)₂, CSA, CH₂Cl₂, room temperature; (vii) K₂CO₃, MeOH, room temperature; (viii) DMSO, (COCl)₂, CH₂Cl₂, Et₃N, -78°C~room temperature (68% from **10a**); (ix) K₂CO₃, MeOH, room temperature; (x) NaBH₄, EtOH, room temperature; (xi) *t*-BuPh₂SiCl, 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 K₂CO₃ in MeOH smoothly took place giving isomeric *syn*-aldehyde (**13**), which upon treatment with NaBH₄ 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

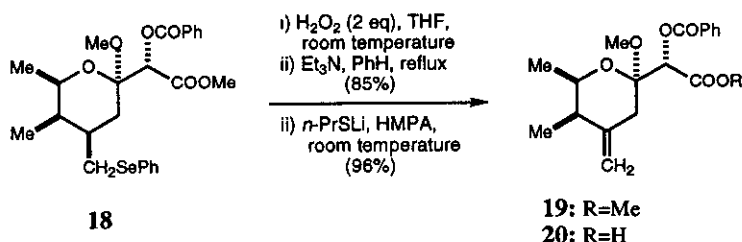
Using the route previously described,⁶ the acetonide (**11**) was converted into the diacetate (**14**) via the α,β -unsaturated ketone (**4**). The right half azide (**5**) was then synthesized from **14** with a small modification of the previous route,⁶ which was more suitable for large-scale preparation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



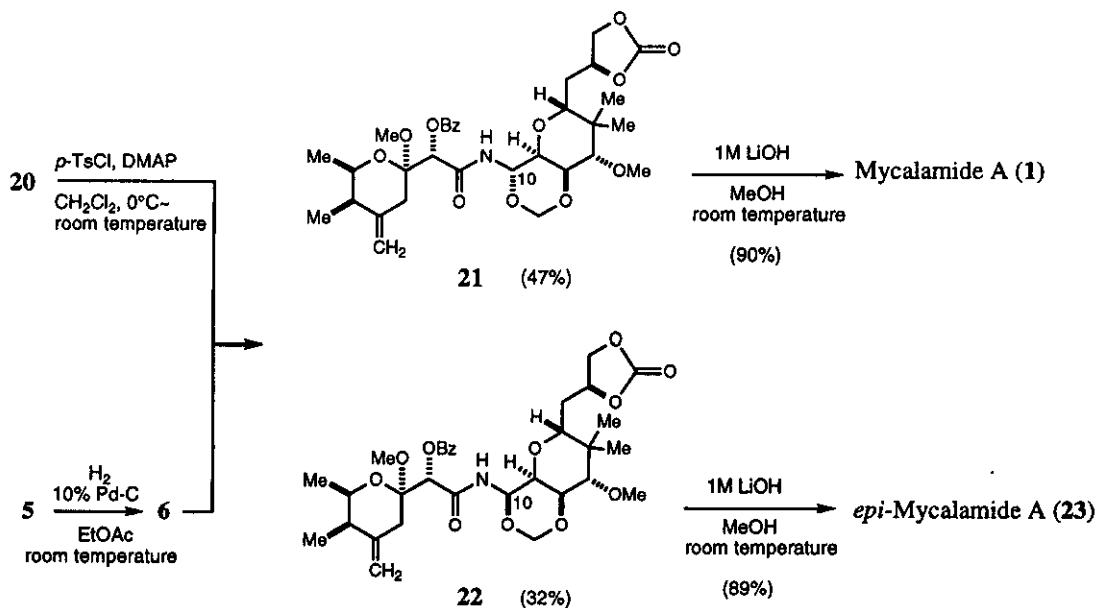
Reagents and Conditions: (i) AcOH-H₂O (10:1), 60°C, 20min; (ii) Ac₂O, pyridine, room temperature (92% from **14**); (iii) PropargylTMS, TMSOTf, MeCN, 0°C (76%); (iv) K₂CO₃, MeOH, room temperature; (v) Im₂CO, THF, room temperature (91% from **16**); (vi) O₃, CH₂Cl₂, -78°C; Me₂S, -78-0°C; (vii) (CH₂O)_n, CSA, CH₂Cl₂, 0°C; (viii) Ac₂O, pyridine, room temperature; (ix) TMSN₃, 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 K₂CO₃ in MeOH followed by 1,1'-carbonyldiimidazole (Im₂CO) 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 Ac₂O, and (4) introduction of azide with TMSN₃.

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 H₂O₂ in THF followed by Et₃N 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**.



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 (^1H nmr, ir, $[\alpha]_D$) of the synthetic **1** were identical with those of mycalamide A synthesized by Kishi.⁴

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

1. (a) N. B. Perry, J. W. Blunt, M. H. G. Munro, and L. K. Pannell, *J. Am. Chem. Soc.*, 1988, **110**, 4850; (b) N. B. Perry, J. W. Blunt, M. H. G. Munro, and A. M. Thompson, *J. Org. Chem.*, 1990, **55**, 223.
2. (a) S. Sakemi, T. Ichiba, S. Kohmoto, G. Saucy, and T. Higa, *J. Am. Chem. Soc.*, 1988, **110**, 4851; (b) N. Fusetani, T. Sugawara, and S. Matsunaga, *J. Org. Chem.*, 1992, **57**, 3828; (c) S. Matsunaga, N. Fusetani, and Y. Nakao, *Tetrahedron*, 1992, **48**, 8369.
3. (a) C. Cardani, D. Ghiringhelli, R. Mondelli, and A. Quilico, *Tetrahedron Lett.*, 1965, 2537; (b) T. Matsumoto, M. Yanagiya, S. Maeno, and S. Yasuda, *Tetrahedron Lett.*, 1968, 6297.; (c) A. Furusaki, T. Watanabe, T. Matsumoto, and M. Yanagiya, *Tetrahedron Lett.*, 1968, 6301.
4. (a) C. Y. Hong and Y. Kishi, *J. Org. Chem.*, 1990, **55**, 4242; (b) C. Y. Hong and Y. Kishi, *J. Am. Chem. Soc.*, 1991, **113**, 9693.
5. (a) W. R. Roush and T. G. Marron, *Tetrahedron Lett.*, 1993, **34**, 5421; (b) R. W. Hoffmann and A. Schlapbach, *Tetrahedron Lett.*, 1993, **34**, 7903; (c) T. G. Marron and W. R. Roush, *Tetrahedron Lett.*, 1995, **36**, 1581.
6. T. Nakata, H. Matsukura, D. Jian, and H. Nagashima, *Tetrahedron Lett.*, 1994, **35**, 8229.
7. H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.

8. K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.
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
11. G. A. Crispino, K.-S. Jeong, H. C. Kolb, Z.-M. Wang, D. Xu, and K. B. Sharpless, *J. Org. Chem.*, 1993, **58**, 3785.
12. In the former synthesis,⁶ the overall yield of **11** from the epoxide (**7**) was 43% in six steps.
13. (a) T. Nakata, S. Nagao, N. Mori, and T. Oishi, *Tetrahedron Lett.*, 1985, **26**, 6461; (b) T. Nakata, S. Nagao, and T. Oishi, *Tetrahedron Lett.*, 1985, **26**, 6465.
14. A. M. Thompson, J. W. Blunt, M. H. G. Munro, and B. M. Clark, *J. Chem. Soc., Perkin Trans. 1*, 1994, 1025.

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