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Synthesis of the Right Half of Mycalamide A. A Formal Total Synthesis

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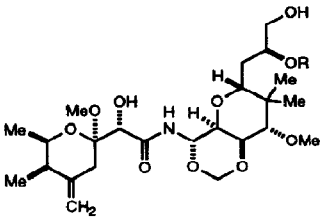
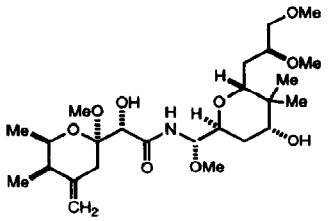
Abstract: The right half **5** of Mycalamide A (**1**) was synthesized *via* α,β-unsaturated ketone **11** which was prepared starting from (*S*)-malic acid or (*R*)- and (*S*)-pantolactones, stereoselectively.

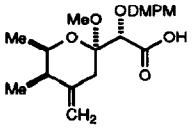
Mycalamide A (**1**) and B (**2**), isolated from a New Zealand sponge of the genus *Mycale*, exhibit potent antiviral and antitumor activities.[1] The structure of **1** and **2** is strikingly similar to that of pederin (**3**), a strong insect poison isolated from *Paederus fuscipes*.[2] The structurally related compounds, onnamides and theopederins, have also been isolated from marine sponges.[3] The unique structure and potent bioactivity of this family have attracted much attention of synthetic organic chemists.[4,5] Hong and Kishi have reported the first total synthesis of mycalamide A (**1**), B (**2**), and onnamide A.[4] The synthesis of **1** was accomplished *via* the coupling of the left half **4** and the right half **5**; the former was prepared in two steps from one of the intermediates in our total synthesis of pederin[6] and the latter was synthesized starting from methyl α-D-glucopyranoside. We have also engaged the synthesis of this family and now report the synthesis of the right half of mycalamide A (**1**) *via* α,β-unsaturated ketone **11** as the key intermediate.



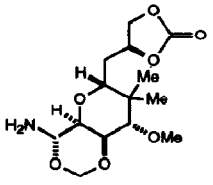
Mycalamide A (**1**) : R = H
Mycalamide B (**2**) : R = Me



Pederin (**3**)



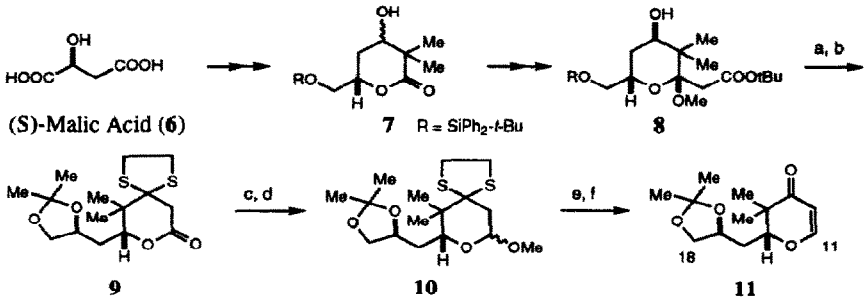
Left half **4**



Right half **5**

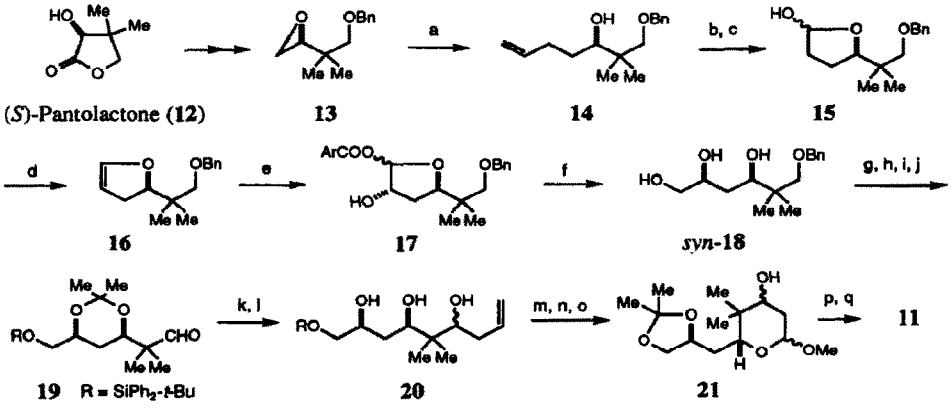
The synthesis of **11** was achieved starting from alcohol **8**,[6a] prepared from (*S*)-malic acid (**6**) *via* lactone **7**. The compound **8** has already been used as an intermediate in the synthesis of the right half of pederin. On treatment of **8** with ethanedithiol and BF_3-Et_2O, acetal-thioacetal interchange, formation of lactone and removal of silyl group took place simultaneously producing δ-lactone,[6a] which was treated with

$Me_2C(OMe)_2$ and CSA to give acetonide **9**. DIBAH reduction of **9** and subsequent acetalization produced methyl acetal **10**, which was treated with NBS followed by *n*-Bu4NF giving α,β-unsaturated ketone **11**.[7]



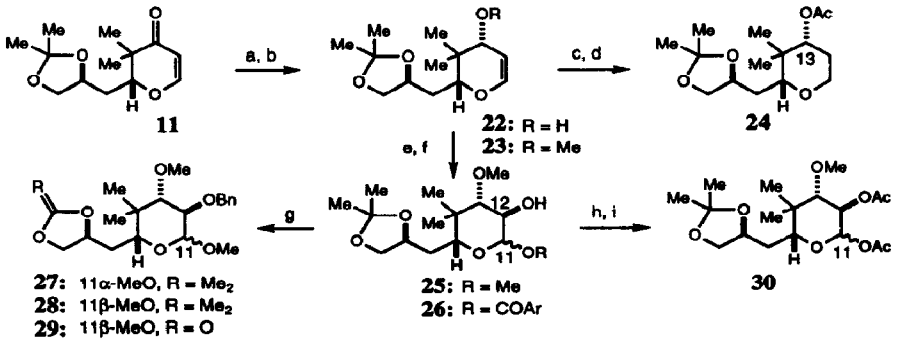
(a) $HSCH_2CH_2SH$, BF_3·Et_2O, CH_2Cl_2, -30°C; (b) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (69% from **8**); (c) DIBAH, toluene, -78°C; (d) $CH(OMe)_3$, CSA, acetone, MeOH, CH_2Cl_2, rt (77% from **9**); (e) NBS, $AgNO_3$, Na_2CO_3, aq MeCN, 0°C; (f) *n*-Bu_4NF, THF, rt (82% from **10**).

An alternative route for the synthesis of the ketone **11** was developed as follows. Reaction of epoxide **13**,[8] prepared from (*R*)- or (*S*)-pantolactone (**12**), with allylmagnesium chloride in the presence of CuI in THF gave alcohol **14**. Olefin **14** was converted into **16** *via* **15** by oxidative cleavage of olefin and subsequent dehydration. Oxidation of **16** with *m*-CPBA afforded alcohol **17** stereoselectively, which was reduced with $LiAlH_4$ producing triol **18** as a separable mixture of *syn*- and *anti*-isomers in a ratio of 14 : 1. The pure *syn*-triol **18** was converted into acetal **21** by nine conventional reactions, whose PDC oxidation followed by *n*-Bu4NF treatment gave the desired α,β–unsaturated ketone **11**.[9]



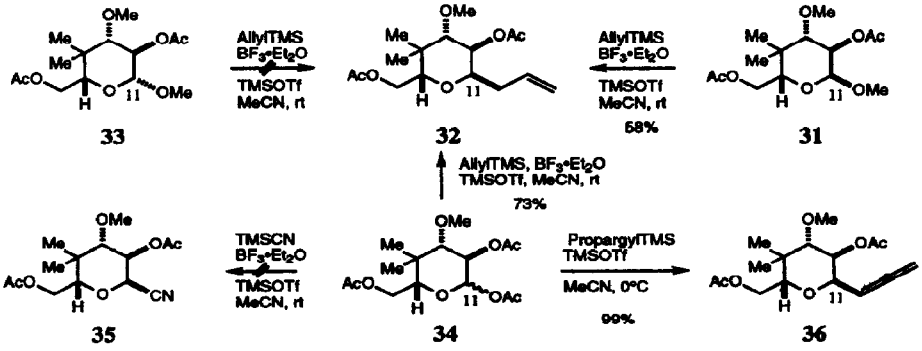
(a) AllylMgCl, CuI, THF, -23°C ~ rt (99%); (b) OsO_4, NMO, aq acetone, *t*-BuOH, rt; (c) $NaIO_4$, aq THF, rt (74% from **14**); (d) MsCl, Et_3N, *i*-Pr_2NEt, CH_2Cl_2, reflux (67%); (e) *m*-CPBA, CH_2Cl_2, rt ; (f) $LiAlH_4$, THF, reflux (84% from **16**); (g) *t*-$BuPh_2SiCl$, imidazole, DMF, rt (92%); (h) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (90%); (i) H_2, $Pd(OH)_2$, THF, rt (85%; 96% based on the consumed benzyl ether); (j) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78°C ~ rt (92%); (k) AllylMgCl, THF, 0°C; (l) AcOH-H_2O (5 : 1), 60°C; (m) O_3, MeOH, -78°C; Me_2S, -78°C ~ rt; (n) $CH(OMe)_3$, CSA, MeOH, rt; (o) $Me_2C(OMe)_2$, CH_2Cl_2, CSA, rt (80% from **19**); (p) PDC, CH_2Cl_2, rt; (q) *n*-Bu_4NF, THF, rt (50% from **21**).

Reduction of **11** with $NaBH_4$-$CeCl_3$ in MeOH gave the single alcohol **22**, which was treated with MeI and KH giving methyl ether **23**. The configuration of the hydroxyl group in **22** was confirmed after the conversion of **22** into the saturated compound **24**; ^1H NMR δ 4.62 (dd, J=6, 11 Hz; C13-H). Oxidation of **23** with *m*-CPBA in MeOH and CH_2Cl_2 produced **25** and **26**, respectively, with complete stereoselection at C12. Benzylation of **25** produced **27** and **28** (1.2 : 1) which were separated by silica gel column chromatography.[10] Alkaline hydrolysis of **26** followed by acetylation gave an inseparable mixture of diacetates **30**.

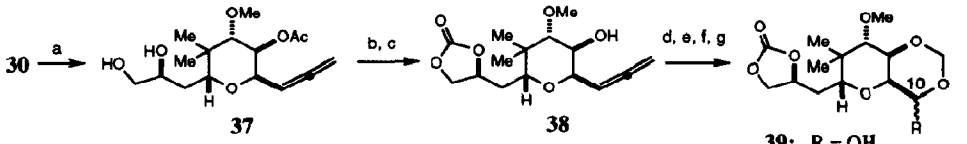


(a) $NaBH_4$, $CeCl_3$, MeOH, -78°C – rt; (b) MeI, KH, THF, 0°C (90% from **11**); (c) H_2, 10% Pd-C, MeOH, rt; (d) Ac_2O, pyridine, rt (96% from **22**); (e) *m*-CPBA, MeOH, rt (81%); (f) *m*-CPBA, CH_2Cl_2, rt; (g) BnBr, NaH, DMF; THF, rt (90%); (h) K_2CO_3, MeOH, rt; (i) Ac_2O, pyridine, rt (88% from **23**).

Then, model experiments for the introduction of the carbon side chain into the C11 position were undertaken. Treatment of the 11β(*axial*)-methoxy anomer **31** with allyltrimethylsilane in the presence of BF_3·Et_2O and TMSOTf in MeCN produced the desired **32** having 11β(*axial*)-allyl group,[11] whereas the reaction using the 11α(*equatorial*)-methoxy anomer **33** did not proceed cleanly. On the other hand, from a mixture of 11α- and 11β-diacetates **34** the 11β-allyl isomer **32** was obtained as a single product in 73% yield. An attempt to introduce the cyano group to **34** was unsuccessful,*cf.* [6a] but the allene group could be introduced by applying the reaction used in Kishi's synthesis of **5**.[4a] Namely, when **34** was treated with propargyltrimethylsilane in the presence of TMSOTf in MeCN 11β-allene **36** was obtained in 99% yield. The product **36** should be useful in the synthesis of theopederin E.



Taking into account the above model experiments, **30** was chosen for the further reaction. On treatment of **30** with propargyltrimethylsilane under Kishi's conditions, introduction of the allene group and deprotection of the acetonide group took place simultaneously producing 11β-allene **37** as a single product. Alkaline hydrolysis of **37** followed by Im_2CO treatment gave carbonate **38**, which was treated with ozone and then paraformaldehyde producing lactol **39**. Finally, acetylation of **39** and the subsequent treatment of **40** with $TMSN_3$ in the presence of TMSOTf in MeCN gave the desired azide **41** as an inseparable 1 : 1.1 C10 diastereomeric mixture. ^1H NMR data of **41** were in good accord with those of the authentic sample.[4a] As the total synthesis of mycalamide A (**1**) was accomplished *via* coupling of 4 and **5** prepared from **41** by hydrogenation, this work represents a formal total synthesis of **1**.



(a) Propargyl-TMS, TMSOTf, MeCN, 0°C (73% from **23**); (b) K_2CO_3, MeOH, rt; (c) Im_2CO, benzene, rt (57% from **37**); (d) O_3, MeOH, -78°C; Me_2S, -78°C ~ rt; (e) $(CH_2O)_n$, conc. HCl, benzene, ~10°C; (f) Ac_2O, pyridine, rt; (g) $TMSN_3$, TMSOTf, MeCN, 0°C (48% from **38**).

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7. Data for **11**: mp 40-43°C; IR (neat) 1660, 1590 cm^{-1}; $[\alpha]_D$ +94.3° (c 1.1, $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$) δ 1.04, 1.11, 1.37, 1.43 (each s; Me x 4), 3.62 (t like, J=7.9 Hz; C18-H), 4.05 (dd, J=2.1, 10.4 Hz; C15-H), 4.10 (dd, J=5.8, 7.9 Hz; C18-H), 4.35 (m; C17-H), 5.36 (d, J=5.8 Hz; C12-H), 7.28 (d, J=6.1 Hz; C11-H).
8. The epoxide **13** was synthesized from (*S*)-pantolactone in five steps; 1) $LiAlH_4$, 2) CSA, acetone, 3) BnBr, NaH, 4) aq AcOH, 5) NaH, *p*-TsCl, or from (*R*)-pantolactone in seven steps; 1) $LiAlH_4$, 2) CSA, acetone, 3) BnBr, NaH, 4) aq AcOH, 5) PivCl, py, 6) MsCl, py, 7) K_2CO_3, MeOH. See also, Lavallee, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679.
9. The alternative route was rather suitable for large-scale preparation of **11**: the thioacetalization of **8** with ethanedithiol in the first route gave unsatisfied results for large-scale reaction.
10. 11β-Methoxy isomer **28** was converted into the corresponding carbonate **29**, the key intermediate in Kishi's synthesis of **5**, in two steps; 1) *p*-TsOH, MeOH, 2) Im_2CO, benzene. ^1H NMR data of the synthetic **29** were identical with those of the authentic sample.[4a]
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