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Total Synthesis of the 7,10-Epimer of the Proposed Structure of Amphidinolide N, Part II: Synthesis of C17–C29 Subunit and Completion of the Synthesis

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Abstract: The total synthesis of 7,10-epimer of the proposed structure of amphidinolide N was accomplished. The requisite chiral C17–C29 subunit was assembled stereoselectively via Keck allylation, Shi epoxidation, diastereoselective 1,3-reduction, and a later oxidative synthesis of the THF framework. The C1–C13 and C17–C29 subunits were successfully coupled using a Enders RAMP "linchpin" as the C14–C16 three carbon unit, thereby controlling the chirality at C14 and C16. The labile allyl epoxy moiety was successfully constructed by Grieco–Nishizawa olefination at a final stage of the synthesis.

In the preceding paper in this issue,[1] we described that 7,10-epimer of the proposed structure of amphidinolide N (**4**) could be disconnected into three subunits **7**, **8** and **9** (Scheme 1), and further described the synthesis of the C1–C13 subunit **7** via a highly enantioselective and diastereoselective route. In this paper, we report the synthesis of the C17–C29 subunit **9** and a RAMP-Enders-based coupling of the three units to complete the total synthesis of the macrolide **4**.

First of all, the synthesis of C17–C29 subunit **9** will be described. The retrosynthesis is shown in Scheme 1. The THF ring of **9** would be obtained via intramolecular oxidative cyclization of **1**, triggered by DDQ. The *anti* 1,3-diol of **1** would be formed by diastereoselective *anti*-reduction of β-hydroxy ketone **2**.[2] Ketone **2** would be obtained by alkynylation of **3** with **6**. The known aldehyde **5**[3] would be converted into chiral aldehyde **3** by Keck asymmetric allylation.[4] On the other hand, the terminal alkyne **6** would be derived from **10** via epoxide opening followed by intramolecular oxidative cyclization. The chiral epoxide **10** would be synthesized by Shi asymmetric epoxidation[5] of the corresponding *trans*-enyne, which would be readily prepared from commercially available alkyne **11**.[6]

Our synthetic route to the chiral aldehyde **3** is illustrated in Scheme 2. Keck asymmetric allylation[4] of the known aldehyde **5**[3] with allylstannane proceeded in the presence of 10 mol% of (*S*)-BINOL and $Ti(OiPr)_4$. This afforded the chiral homoallyl alcohol **12** in excellent yield with excellent enantioselectivity. The hydroxy group of **12** was protected by TBS to give **13**. Dihydroxylation of double bond followed by oxidative cleavage of the resulting diol afforded aldehyde **3** in good yield.

Synthesis of the terminal alkyne **6** began by converting the commercially available **11** to *trans*-vinyl iodide **14** according to the literature procedure[6] (Scheme 3). Sonogashira coupling[7] of vinyl iodide **14** with trimethylsilylacetylene gave enyne **15** in good yield. The enantioselective epoxidation of **15** was accomplished by the method of Shi using organocatalyst **16** to give the chiral epoxide **10** in moderate yield and good enatioselectivity, which was determined in the next step.[5] The chiral epoxide **10** was converted into alcohol **17** via regioselective epoxide opening with 3,4-dimethoxybenzyl alcohol as a nucleophile in the presence of CSA as catalyst. The desired **17** could not be obtained when Lewis acids such as $BF_3{\cdot}Et_2O$, $Ti(OiPr)_4$, and $Sc(OTf)_3$ were employed instead of CSA.[8] Removal of the TMS group of **17** afforded **18**. Oxidative acetal formation was accomplished by the treatment of 3,4-dimethoxybenzyl ether **18** with DDQ under anhydrous conditions to afford acetal **6** in moderate yield.

Synthesis of the intermediate **1** is shown in Scheme 4. First, we attempted to construct the C21 stereocenter via reagent-controlled alkynylation as reported by Shibasaki.[9] However, the method was found ineffective between **6** and **3**, which possess several functional groups, and resulted in recovery of the starting materials. Therefore, we decided to construct the C21 stereogenic center under substrate control. Alkynylation of **3** with lithium acetylide of **6** afforded **19** as a diastereomeric mixture in good yield. TBS deprotection of secondary alcohol followed by MnO_2 oxidation gave β-hydroxy ketone **21**. Ketone **21** was reduced to **2** by alkyne hydrogenation and carbonyl diastereoselective hydride addition with $Me_4NBH(OAc)_3$.[2] This

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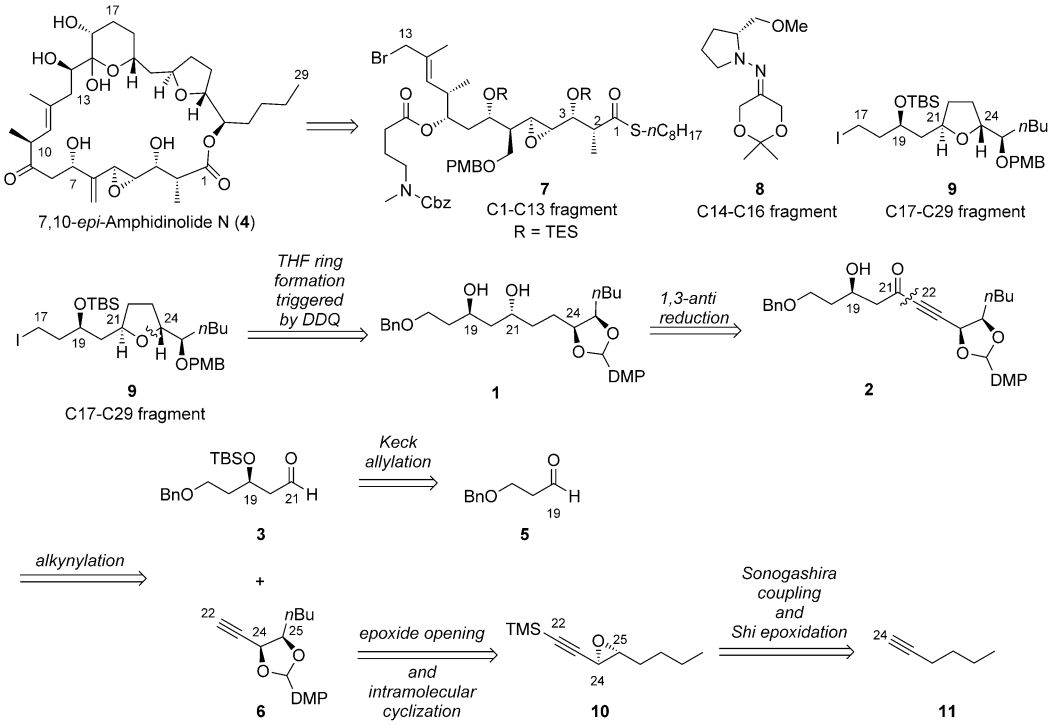
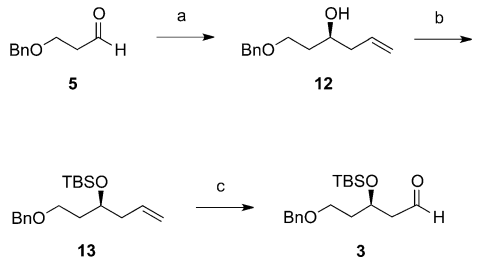
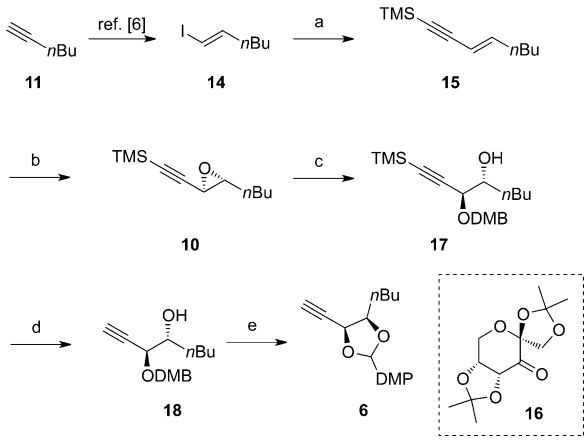


Scheme 1. Retrosynthesis of 7,10-*epi*-amphidinolide N (**4**) and the C17–C29 subunit **9**, Cbz = benzyloxycarbonyl, PMB = *p*-methoxybenzyl, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, Bn = benzyl, DMP = 3,4-dimethoxyphenyl, TMS = trimethylsilyl.



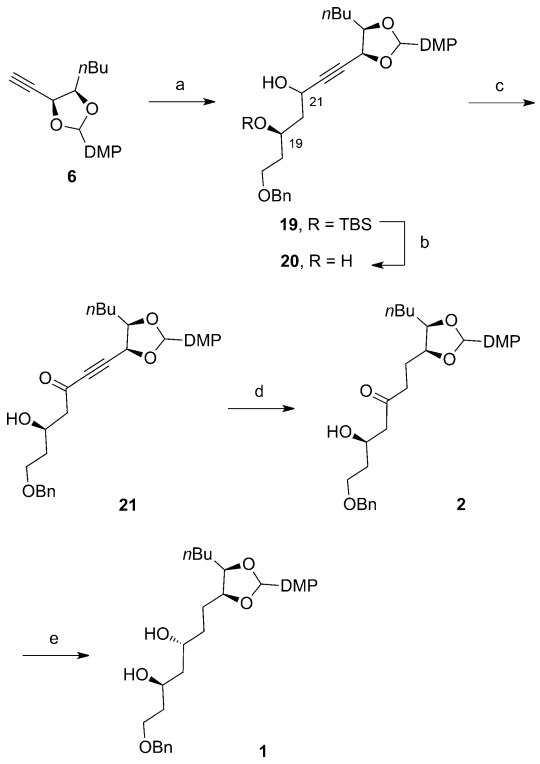
Scheme 2. Synthesis of aldehyde **3**. a) allyltributyltin, Ti(O*i*Pr)$_4$, (*S*)-BINOL, MS4 Å/DCM, −20 °C, quant. (99% *ee*); b) TBSCl, imdiazole/DMF, RT, 96%; c) OsO_4, NMO/dioxane, H_2O, RT then $NaIO_4$, RT, 90%. Bn = benzyl, BINOL = 1,1′-bi-2-naphthol, MS = molecular sieves, TBS = *tert*-butyldimethylsilyl, NMO = *N*-methyl morpholine *N*-oxide.



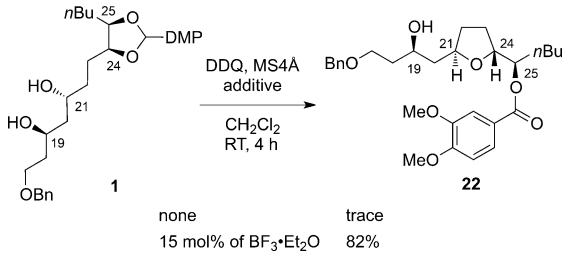
Scheme 3. Synthesis of terminal alkyne **6**. a) TMSC≡CH, Pd(Ph$_3$P)$_4$, Et$_2$NH/DMF, RT, 80%; b) **16**, Oxone, K_2CO_3/DMM, MeCN, 0 °C, 65%; c) 3,4-dimethoxybenzyl alcohol, CSA/DCM, 59% (87% *ee*); d) K_2CO_3/MeOH, RT, 75%; e) DQQ, MS4 Å/DCM, 0 °C, 61%. TMS = trimethylsilyl, DMM = dimethoxymethane, CSA = camphorsulfonic acid, DMB = 3,4-dimethoxybenzyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, MS = molecular sieves, DMP = 3,4-dimethoxyphenyl.

sequence and order of reduction gave the desired *anti*-diol **1** as a single isomer in excellent yield; otherwise, hydride addition of **21** with $Me_4NBH(OAc)_3$ gave almost no diastereoselectivity.

Next, we studied the oxidative THF ring formation using DDQ from **1** (Scheme 5). To the best of our knowledge, an oxidative THF ring formation of this type using DDQ has not been reported.[10] At first, the reaction of **1** with DDQ in the presence of molecular sieves resulted in almost full recovery of the starting material. Therefore, we investigated the effect of additives in the expectation to promote the oxidation, and it was found that the selection and amount of additive were both crucial for successful THF ring formation: for example, a low yield of **22** was observed in the presence of Brønsted acid such as PPTS and CSA. Although an equimolar amount of $BF_3{\cdot}Et_2O$ was found moderately successful, affording the product in moderate yield (59%), optimal results were obtained with a catalytic amount of $BF_3{\cdot}Et_2O$ (15 mol%). Namely, the desired THF derivative **22** was obtained as a single isomer in good yield without formation of the undesired THP ring. Hy-



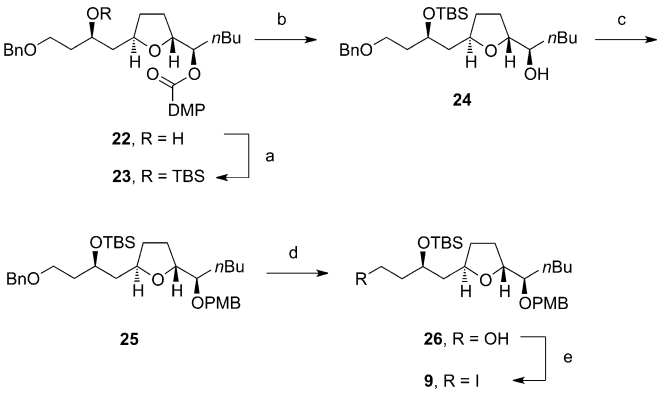
Scheme 4. Synthesis of **1**. a) *n*BuLi/THF, −78 °C, then **3**, −78 °C to RT, 85%; b) TBAF/THF, RT, quant.; c) MnO_2/$CHCl_3$, RT then 50 °C, 75%; d) H_2, Pd-C/EtOAc, RT, 99%; e) $Me_4NBH(OAc)_3$, AcOH/MeCN, −30 °C, 91%. DMP = 3,4-dimethoxyphenyl, Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TBAF = tetra-*n*-butylammonium fluoride.



Scheme 5. THF ring formation triggered by DDQ. Bn = benzyl, DMP = 3,4-dimethoxyphenyl, DDQ = 3,4-dichloro-5,6-dicyano-*p*-benzoquinone, MS = molecular sieves.

droxy group at C21 reacts at C24 position via complete inversion of stereochemistry without reaction at C25. Thus, we have established the novel and efficient method for the THF ring formation.

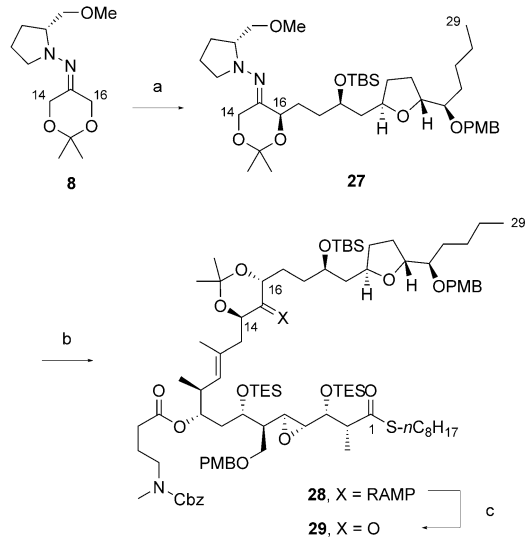
Synthesis of the C17–C29 subunit **9** from **22** is summarized in Scheme 6. TBS protection of secondary alcohol gave **23**. We considered the 3,4-dimethoxybenzoyl group to be too labile under various conditions during the total synthesis, especially during the RAMP hydrazone diastereoselective alkylation stage.[11] Therefore, it was converted into a PMB ether via a two-step procedure. Thus, treatment of **23** with NaOMe followed by PMB protection[12] of the resulting secondary alcohol afforded **25**. Selective Bn etherification of **25** was accomplished



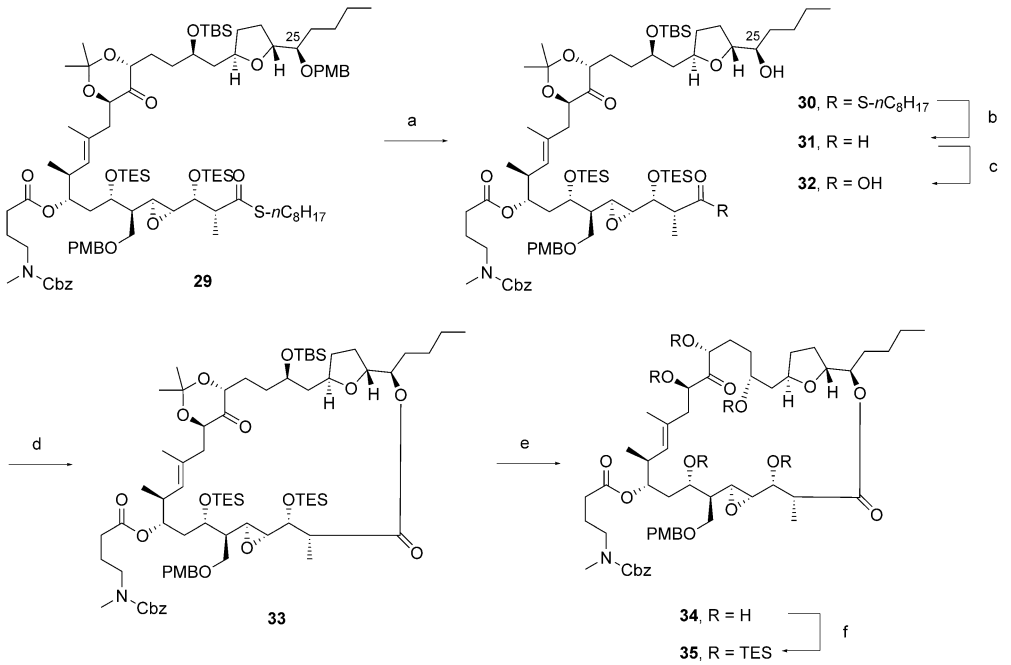
Scheme 6. Synthesis of the C17-C29 subunit **9**. a) TBSOTf, 2,6-lutidine/DCM, RT, 96%; b) NaOMe/MeOH, reflux, 91%; c) PMBOC(=NH)CCl_3, TfOH/Et_2O, RT; d) H_2, Raney Ni (W-2)/EtOH, RT, 54% (2 steps); e) I_2, Ph_3P, imidazole/benzene, RT, 94%. Bn = benzyl, DMP = 3,4-dimethoxyphenyl, PMB = *p*-methoxybenzyl.

without affecting the PMB ether by hydrogenation with Raney nickel to give the primary alcohol **26** in moderate yield.[13] Finally, iodination of primary alcohol with PPh_3 and I_2 gave the desired C17–C29 subunit **9**.

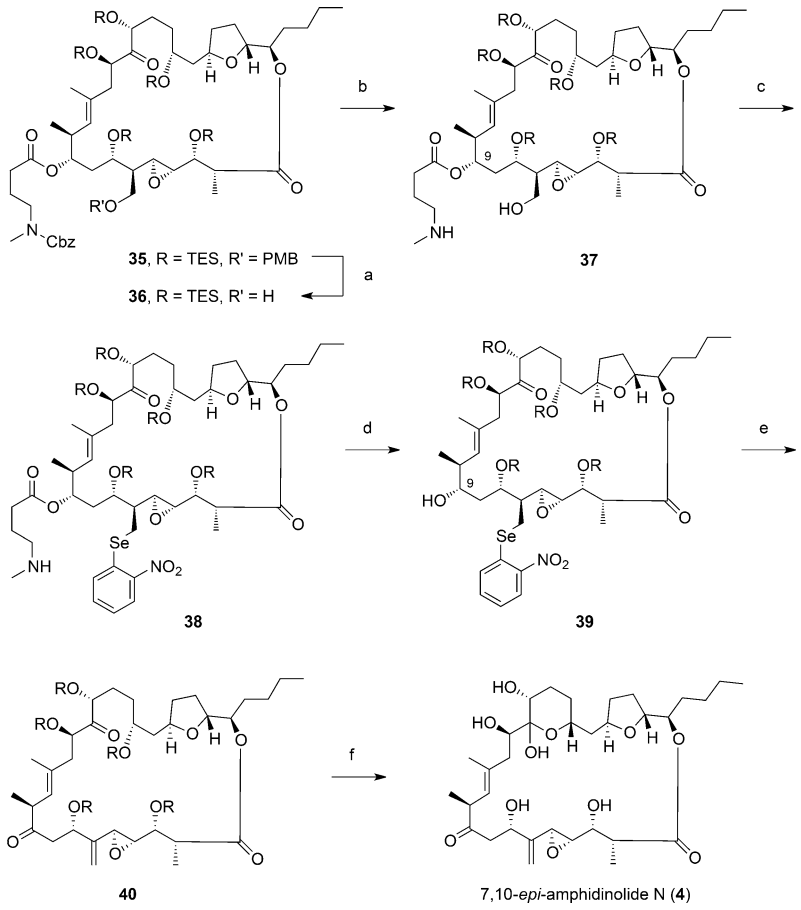
Next, we began to install the full carbon framework of our target molecule **4** by using Enders RAMP hydrazone diastereoselective method via double alkylation of the readily prepared[11,14] three carbon unit of C14–C16 (Scheme 7). The sequential alkylation of hydrazone **8**, first with the C17–C29 subunit **9** and then with the C1–C29 subunit **7**, followed by removal of the chiral auxiliary under mild conditions,[15] gave **29** in good yield over three steps. It is noteworthy that our novel protective C9-hydroxyl ester group[1] was inert under these conditions.



Scheme 7. Segment coupling by RAMP hydrazone diastereoselective alkylation. a) *t*BuLi/THF, −78 °C then **9**, −78 °C; b) *t*BuLi/THF, −78 °C then **7**, −78 °C; c) sat. $(COOH)_2$ aq./Et_2O, RT, 73% (3 steps). RAMP = (*R*)-(+)-1-amino-2-methoxymethylpyrrolidine, TBS = *tert*-butyldimethylsilyl, PMB = *p*-methoxybenzyl, Cbz = benzyloxycarbonyl, TES = triethylsilyl.



Scheme 8. Synthesis of **35**. a) DDQ/DCM, phosphate buffer, 0 °C, 67 %; b) Pd-C, Et_3SiH/DCM, RT; c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene/*t*BuOH, THF, H_2O, 0 °C, 64 % (2 steps); d) 2,4,6-trichlorobenzoyl chloride, Et_3N/toluene, RT then DMAP, RT, 80 %; e) HF aq./MeCN, DCM, 0 °C; f) TBSOTf, 2,6-lutidine/DCM, −78 °C, 37 % (2 steps). TBS = *tert*-butyldimethylsilyl, Cbz = benzyloxycarbonyl, PMB = *p*-methoxybenzyl, TES = triethylsilyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone.



Scheme 9. Total synthesis of **4**. a) DDQ, 2,6-di-*t*Bu-pyridine/DCM, H_2O, 0 °C, 50 %; b) $HCOONH_4$/THF, EtOH, 50 °C, 64 %; c) *o*-nitrophenylseleno cyanate, nBu_3P/benzene, 75 °C; d) xylene, 120 °C; e) TPAP, NMO, MS4 Å/DCM, RT; f) NH_4F/MeOH, RT, 10 % (4 steps). Cbz = benzyloxycarbonyl, PMB = *p*-methoxybenzyl, TES = triethylsilyl, DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, TPAP = tetra *n*-propylammonium perruthenate, NMO = *N*-methylmorpholine *N*-oxide, MS = molecular sieves.

Synthesis of **35** is illustrated in Scheme 8. To our delight, when **29** was treated with 1 equiv of DDQ, selective deprotection of the PMB ether of the secondary alcohol at C25 was realized, without removal of the PMB ether of the primary alcohol, to afford the needed alcohol **30** in 67% yield with recovery of starting material (18%). The selective deprotection of the PMB ether of the secondary alcohol, over that of a primary alcohol, can be ascribed to steric crowdedness around the primary PMB ether moiety. The thioester hydrolysis into carboxylic acid was found to be troublesome. As the desired carboxylic acid **32** was low yielding under various conditions, **30** was converted into the macrolactone precursor **32** in a two-step procedure consisting of Fukuyama's reduction[16] followed by Pinnick–Kraus oxidation of the resulting aldehyde.[17] Yamaguchi macrolactonization[18] of **32** successively proceeded to furnish **33** in good yield. Treatment of **33** with aqueous HF promoted concomitant removal of the acetal protecting group and all silyl protecting groups to afford the pentaol **34**. All hydroxyl groups thus generated were TES protected to afford **35**, which would be removed under mild conditions at the last stage of the synthesis.

The final stage to complete the total synthesis of targeted **4** is shown in Scheme 9. Removal of the PMB-protecting group was performed by treatment of **35** with DDQ in the presence of 2,6-di-*tert*-pyridine to afford **36** along with recovery of the starting material (40%). Cbz deprotection was achieved by treatment of **36** with $HCOONH_4$ and Pd-C in THF/EtOH. Here, the amine generated was anticipated to react with the ester moiety in an intramolecuar fashion to release the alcohol at C9 and 1-methyl-2-pyrrolidone. In this case, however, the C9 alcohol remained protected. Thus, after introduction of *o*-nitrophenylselenyl group to give **38**,[19,20] heating of the xylene solution of **38** at 120 °C under neutral conditions removed the protecting group at C9 to afford alcohol **39**. Next, TPAP oxidation[21] not only led to the oxidative elimination of the selenide via its selenoxide to the labile allyl epoxide, but also oxidized the C9 secondary alcohol to its ketone **40**. Final global desilylation with NH_4F in MeOH[22] gave 7,10-epimer of the proposed structure of amphidinolide N (**4**).

In summary, the asymmetric total synthesis of 7,10-epimer of the proposed structure of amphidinolide N was accomplished. The chiral C17–C29 subunit was stereoselectively synthesized by Keck allylation, Shi epoxidation, and diastereoselective 1,3-reduction as the key steps. The chiral THF ring was constructed by a new oxidative cyclization tactic using DDQ. The assembly of C1–C13 and C17–C29 subunits were successively performed using Enders RAMP methodology as a C14–C16 three carbon "linchpin" unit, thereby defining the new stereogenic centers at C14 and C16. Notably, the new protecting group 4-(*N*-benzyloxycarbonyl-*N*-methylamino)butyryl group was found effective for the C9 alcohol position. Lastly, the labile allyl epoxy moiety was successfully constructed by Grieco-Nishizawa olefination at a late stage of the synthesis.

Keywords: Enders RMAP · Grieco-Nishizawa olefination · Keck allylation · Shi-epoxidation · total synthesis

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