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A Concise Total Synthesis of Amphidinolide T2

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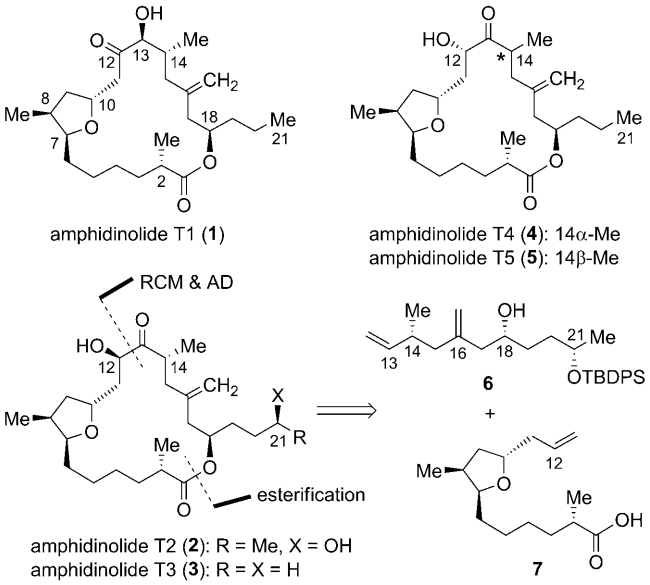
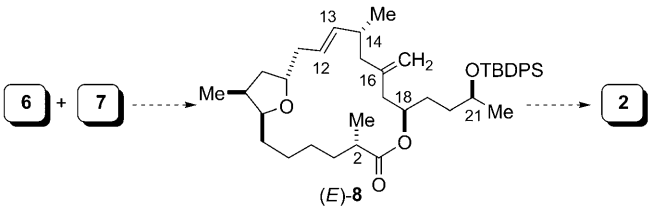
Dedicated to the memory of Professor Xian Huang

Amphidinolides T1–T5 (**1**–**5** in Scheme 1) are 19-membered ring macrolides isolated from symbiotic marine dinoflagellate *Amphidinium* sp.[1,2] and their structures were determined, including an X-ray crystal structural analysis of **1**.[2c] Cytotoxicity was reported for **1**–**4** with IC_{50} values of 7.0–18 and 10–35 $\mu g\,mL^{-1}$ against murine lymphoma L1210 and human epidermoid carcinoma KB cells, respectively.[2b] These amphidinolide T congeners commonly possess an "α-hydroxy ketone" subunit at C12 and C13 and are distinguishable from each other by the relative position and absolute configuration of the C12/C13 hydroxy and the C14 methyl groups (except for the side chain of **2**). The close structural relationship is illustrated by the base-promoted epimerization of **4** into **5**.[2c] Total synthesis of amphidinolide T1 and T3–T5 has been accomplished by several leading laboratories,[3–7] along with synthesis of the C1−C12[8] and the C13−C22 (for **2**) fragments.[5c] As the continuation of our total synthesis of amphidinolide X and Y,[9] we report herein the total synthesis of amphidinolide T2 (**2**) from fragments **6** and **7**[5b,8b] by using a key sequence of ring-closing metathesis (RCM)[10] and asymmetric dihydroxylation (AD)[11] to assemble the C12/C13 "α-hydroxy ketone" subunit (Scheme 1).[12]



Scheme 1. Structures of amphidinolide T1–T5 (**1**–**5**) and the fragments **6** and **7** for total synthesis of amphidinolide T2 (**2**) by RCM and AD. TBDPS = *tert*-butyldiphenylsilyl.

Three ring-formation methods have been used in the total synthesis of amphidinolide T1 and T3–T5.[13] Besides the classical macrolactonization,[4,6,7] Fürstner et al. assembled the 19-membered ring between C4 and C5 by RCM–hydrogenation.[3] Alternatively, Jamison et al. utilized the Ni-catalyzed reductive macrolactonization of the *seco* alkynyl aldehyde to form the C12–C13 sp^3–sp^3 bond with concomitant installation of the masked "α-hydroxy ketone" subunit.[5] For our synthesis, given in Scheme 2, we should achieve 1) regio- and diastereoselective RCM between C12 and C13



Scheme 2. Proposed formation of (*E*)-**8** by RCM and conversion into **2**.

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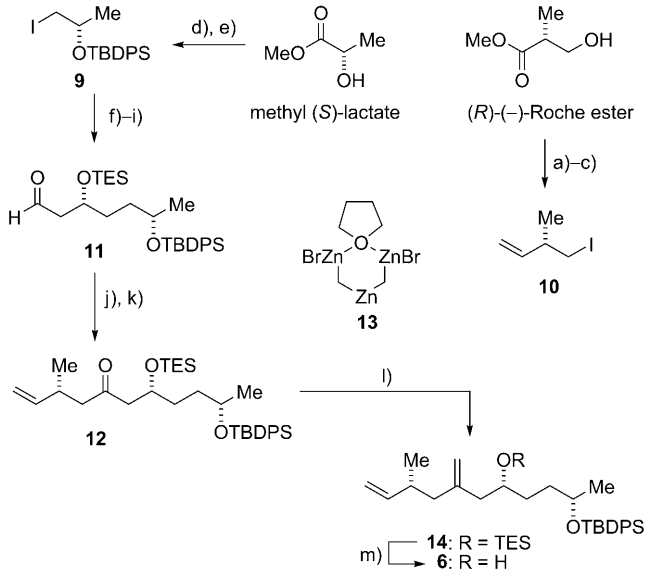
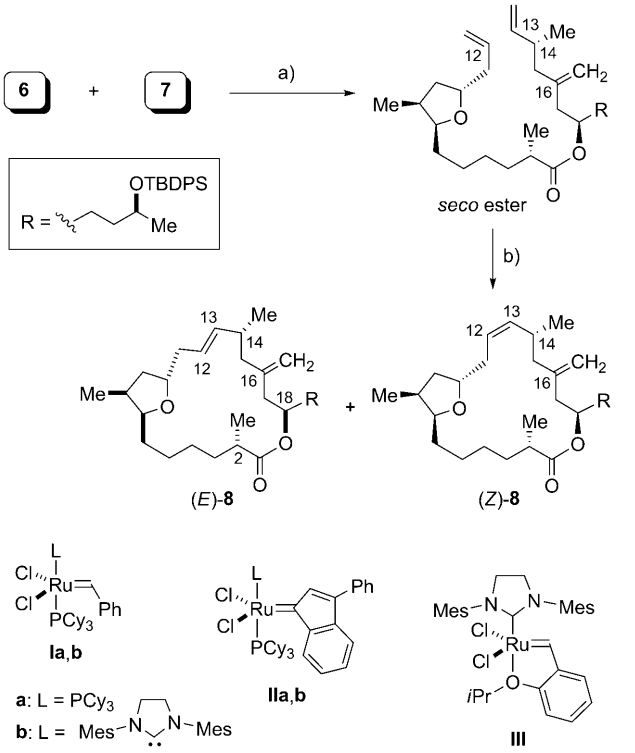
in the presence of the C16 methylene group; 2) regio- and diastereoselective dihydroxylation of the endocyclic C12=C13 double bond in (*E*)-**8** in the presence of the C16 exocyclic methylene group; and 3) regioselective oxidation of the C13 hydroxy group in the 12,13-diol. We envisaged that the relatively low reactivity of the 1,1-disubstituted double bond in RCM[14] might provide the basis for our required regioselectivity in the ring formation. In contrast, selective dihydroxylation of 1,2-disubstituted alkenes over 1,1-disubstituted counterparts is very rare.[11b] We expected that the substituents and ring conformation may be helpful for "shielding" the C16 methylene group during AD after inspecting the crystal structure of **1**.[2c]

Scheme 3 shows the synthesis of the diene alcohol **6**. The chiral iodide **9** was obtained from methyl (*S*)-lactate in 92% overall yield through protection of the hydroxy group as the TBDPS ether, reduction of the ester moiety by $BH_3{\cdot}SMe_2$, and conversion of the hydroxy group into the iodide in the presence of I_2, PPh_3, and imidazole. It was then transformed into the aldehyde **11** in 72% overall yield in four steps: 1) alkylation of methyl acetoacetate with **9**; 2) enantioselective hydrogenation of the β-ketone ester;[15] 3) TES ether formation; and 4) controlled DIBAL-H reduction of the ester moiety. On the other hand, the chiral iodide **10** was prepared by a modified procedure from methyl (*R*)-(−)-3-hydroxy-2-methylpropionate (Roche ester) in 76% overall yield by tosylation, partial ester reduction, Wittig-type methylenation, and iodide replacement of the tosylate. Addition of the alkyllithium prepared from **10** with the aldehyde **11** gave, after DMP oxidation, the ketone **12**. The latter was treated with the Nysted's reagent **13**[16] to directly afford the diene alcohol **6** (76%) as the major product along with the TES ether **14** (16%), suggesting that the TES ether **14** underwent partial cleavage under the Lewis acidic conditions. Upon exposure to TFA/H_2O/THF (1:4:100, RT, 2.5 h), the TES ether **14** was converted into the alcohol **6** in 90% yield.



Scheme 3. Synthesis of the alcohol fragment **6**. a) 4-Toluenesulfonyl chloride (TsCl), 4-dimethylaminopyridine (DMAP), Et_3N, CH_2Cl_2, RT, 12 h, 98%; b) i) diisobutylaluminum hydride (DIBAL-H), PhMe, −90 °C, 1 h; ii) *n*BuLi, $MeP^+Ph_3Br^-$, THF, 0 °C, 0.5 h, 83% (2 steps); c) LiI, Et_2O, reflux, 4 h, 94%; d) TBDPSCl, imidazole, THF, RT, 2 h, 99%; e) i) $BH_3{\cdot}SMe_2$, THF, reflux, 2 h; ii) I_2/PPh_3/imidazole (4:2:4), THF, reflux, 1 h, 93% (2 steps); f) methyl acetoacetate, NaH, *n*BuLi, THF/hexamethylphosphoric triamide (HMPA) (3:1), 0 °C; **9**, RT, 4 h, 59% (82% based on reacted starting material (brsm)); g) [$RuBr_2${(*R*)-BINAP}] (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), MeOH, 60 °C, 6 h, 90%; h) triethylsilyl trifluoromethanesulfonate (TESOTf), 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 99%; i) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 99%; j) **10**, *t*BuLi, pentane/Et_2O (3:2), −78 °C, 0.5 h and −20 °C, 0.5 h, then **11**, −78 °C, 2 h, 70% (82% brsm); k) Dess–Martin periodinane (DMP), $NaHCO_3$, RT, 2 h, 87%; l) **13**, $TiCl_4$, THF, reflux, 0.5 h, 76% **6**, 16% **14**; m) trifluoroacetic acid (TFA)/H_2O/THF (1:4:100), RT, 2.5 h, 90%.

We obtained the acid fragment **7** through a nine-step sequence by using the SmI_2-mediated enantioselective reductive coupling of the (1*S*,2*R*)-*N*-methylephedrine-derived crotonate with aldehydes to secure the *cis* stereochemistry at C7/C8 on the tetrahydrofuran ring.[8b] As shown in Scheme 4, the alcohol **6** and the acid **7** were condensed to give the *seco* ester, which was then treated with Grubbs second-generation initiator **Ib** (5 mol%) in CH_2Cl_2 at reflux for 4 h, affording the macrolactones (*E*)-**8** (63%) and (*Z*)-**8** (23%) (entry 2, Table 1). We were pleased to achieving high regioselectivity in the RCM reaction without affecting the C16 methylene group. To improve the *E*/*Z* ratio, the RCM reaction was carried out in different solvents. A remarkable solvent effect was found; by using **Ib** only the *seco* ester was



Scheme 4. Synthesis of macrolactones (*E*)-**8** and (*Z*)-**8** by RCM. a) 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), DMAP, RT, 16 h, 91%; b) 5 mol% **Ib**, CH_2Cl_2, reflux, 4 h, 63% (*E*)-**8**, 23% (*Z*)-**8**. Mes = 2,4,6-trimethylphenyl.

Table 1. Results of RCM of the *seco* ester and attempted isomerization of (*Z*)-**8**.

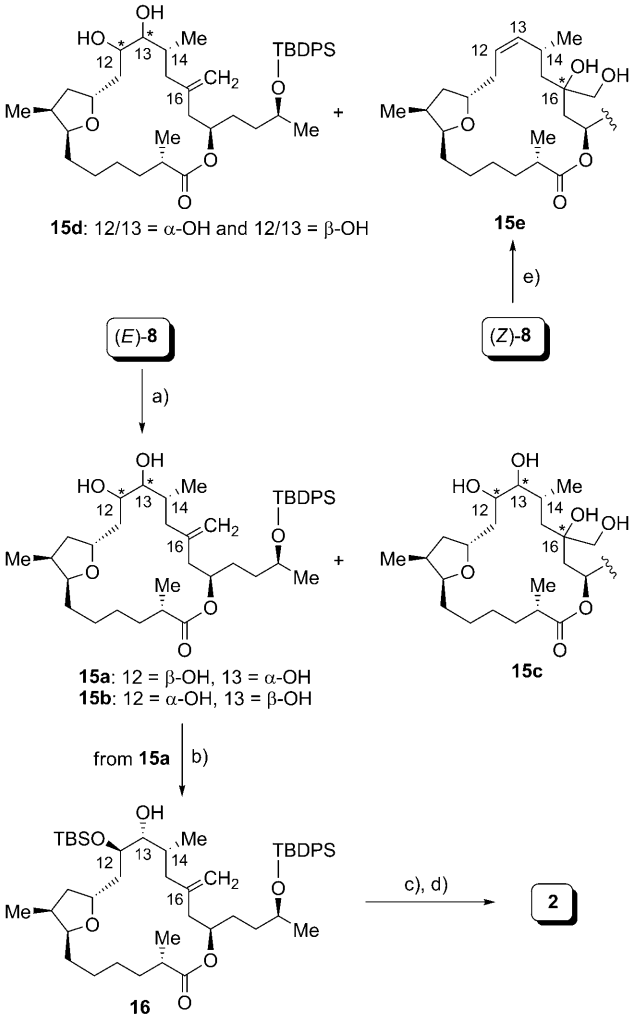
	Substrate	Reaction conditions[a]	Products (Yield [%])[b]
1	*seco* ester	**Ia**, 15 h[c]	–[d]
2	*seco* ester	**Ib**, 4 h	(*E*)-**8** (63), (*Z*)-**8** (23)
3	*seco* ester	**IIa**, 5 h	–[e]
4	*seco* ester	**IIb**, 10 h	(*E*)-**8** (60), (*Z*)-**8**[f] (21)
5	*seco* ester	**III**, 10 h	(*E*)-**8** (60), (*Z*)-**8**[g] (20)
6	(*Z*)-**8**	**Ib**, CH_2Cl_2, 100 °C, 0.5 h, MW	(*E*)-**8**[e] (trace)
7	(*Z*)-**8**	**IIa**, 1 d	–[e]
8	(*Z*)-**8**	I_2 (cat.), 1 d	–[e]

[a] With 5 mol % of the indicated initiator and in CH_2Cl_2 at reflux unless otherwise stated, MW = microwave. [b] Isolated yields. [c] 10 mol % of **Ia**. [d] 60 % of the *seco* ester was recovered. [e] Recovery of the starting materials. [f] 10 % of the *seco* ester was recovered. [g] 11 % of the *seco* ester was recovered.

recovered in hexane after heating at reflux for 8 h, whereas an inseparable mixture of unidentified byproducts was obtained in toluene at 80 °C for 4.5 h[17] (data not shown in Table 1).

The indenylidene ruthenium complexes **IIa**[18] and **IIb**[9c] were reported for the formation of macrocyclic di- and trisubstituted *E*-double bonds possessing α-substituents. We examined the first-generation initiators **Ia** and **IIa** for the RCM reaction, but they failed to form any product with recovery of the *seco* ester (entries 1 and 3, Table 1). In contrast, the second-generation indenylidene-derived initiator **IIb** and Hoveyda–Grubbs second-generation initiator **III** could promote the RCM reaction, but they were less efficient than **Ib**, giving similar ratios for (*E*)-**8** and (*Z*)-**8** (entries 4 and 5 vs. entry 2, Table 1). These results imply that the highly reactive complex **Ib** is the best for assembling the 19-membered ring of amphidinolide T congeners.[3] We then turned our attention to isomerization of the isolated (*Z*)-**8**, but we found that no reaction took place in the presence of the ruthenium complexes **Ib** and **IIa**, and I_2, respectively, in CH_2Cl_2 at reflux for one day or at 100 °C for 0.5 h along with microwave irradiation[19] (entries 6–8, Table 1). These negative results suggest that the RCM reaction in Scheme 4 might be kinetically controlled and the product (*Z*)-**8**, once formed, could not enter into the reverse-reaction pathway.[20] Nevertheless, the diastereoselectivity ($E/Z \approx 73:27$) of our RCM reaction catalyzed by **Ib** is comparable to the results ($E/Z = 67:33$–$86:14$) reported for the RCM reactions between C4 and C5 in the total synthesis of other amphidinolide T congeners.[3]

The next challenging task en route to our target was the installation of the α-hydroxy ketone unit at C12 and C13 in the correct absolute configuration (Scheme 5). Our preliminary results showed that no dihydroxylation of (*E*)-**8** occurred with commercial AD-mix-β alone. When the combination of $K_2OsO_2(OH)_2$ and NMO was used, a complex reaction mixture was obtained, implying that a chiral ligand is essential for selective dihydroxylation (entry 1, Table 2). By using the modified AD-mix-β at room temperature for 8 h, compound (*E*)-**8** was converted into the desired diol **15a** (48 %) and the fully oxidized tetraols **15c** (45 %) along with



Scheme 5. Total synthesis of **2**. a) 2.5 mol % $K_2OsO_2(OH)_4$, 10 mol % $(DHQD)_2AQN$ ($(DHQD)_2AQN$ = hydroquinidine (anthraquinone-1,4-diyl) diether), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C, 7 h, 59 % **15a**, 13 % **15b**, 5 % **15c** (9 % of (*E*)-**8** was recovered); b) *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h, 77 %; c) DMP, $NaHCO_3$, RT, 3 h, 95 %; d) HF·pyridine, MeCN, RT, 16 h, 91 %; e) 5 mol % $K_2OsO_2(OH)_4$, 10 mol % $(DHQ)_2PHAL$ ($(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether), AD-mix-α, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 0 °C, 7 h, 30 % **15d** (as a 50:50 inseparable mixture of two diastereomers), 15 % **15e**, 15 % **15c**.

6 % of the diastereomeric diol **15b** (entry 2, Table 2). When the same AD was performed at 0 °C, formation of the tetraol **15c** was reduced to 18 % yield with an increased yield of the minor diol **15b** (18 %), while the yield of the desired diol **15a** remained similar (entry 3, Table 2). These results might be explained by the following considerations: 1) AD of the C12=C13 endocyclic double bond in (*E*)-**8** is faster than the C16 exocyclic counterpart and the diastereoselectivity (the ratio of **15a**:**15b**) might be temperature insensitive because the isolated yield for **15a** was nearly the same; and 2) further dihydroxylation of the C16 methylene group is much easier for **15b** than **15a** and the reaction rate is temperature dependent, resulting in higher conversion of **15b** at

Table 2. Some results of dihydroxylation of (*E*)-**8** and (*Z*)-**8**.[a]

	Substrate	Chiral ligand	Products (Yield [%])[b]
1	(*E*)-**8**	–[c]	complex mixture
2	(*E*)-**8**	$(DHQD)_2PHAL$[d,e]	**15a** (48), **15b** (6), **15c** (45)
3	(*E*)-**8**	$(DHQD)_2PHAL$[d,f]	**15a** (51), **15b** (18), **15c** (18)
4	(*E*)-**8**	$(DHQD)_2AQN$[f,g]	**15a** (44), **15b** (8), **15c** (18)
5	(*E*)-**8**	$(DHQD)_2AQN$[f–h]	**15a** (59), **15b** (13), **15c**[i] (5)
6	(*Z*)-**8**	$(DHQ)_2PHAL$[f,j]	**15d** (30), **15e** (15), **15c** (15)

[a] Carried out in *t*BuOH/H_2O (1:1) in the presence of $K_2OsO_2(OH)_4$ (5 mol%), the chiral ligand (10 mol%), $MeSO_2NH_2$ (1 equiv), and other additives as stated. [b] Isolated yields. [c] $K_2OsO_2(OH)_4$ (15 mol%) and 4-methyl morpholine *N*-oxide (NMO) (3 equiv) in acetone/H_2O (5:1) at RT for 4 h. [d] AD-mix-β was added. [e] RT, 8 h. [f] 0 °C, 7 h. [g] $MeSO_2NH_2$ (1 equiv), K_2CO_3 (3 equiv), and $K_3Fe(CN)_6$ (3 equiv) were added. [h] 2.5 mol% of $K_2OsO_2(OH)_4$ was used. [i] 9% of (*E*)-**8** was recovered. [j] AD-mix-α was added.

room temperature. If the above argument is correct, the diastereoselectivity for AD of (*E*)-**8** using the chiral ligand $(DHQD)_2PHAL$ should not be higher than 74:26 and the major diol **15a** might be formed from a chirality-matched process.[21]

To improve diastereoselectivity, we tried AD of (*E*)-**8** using $(DHQD)_2AQN$, which is considered as a generally preferred chiral ligand for AD of aliphatic mono-, 1,1-di-, 1,2-(*E*)-di-, tris-, and cyclic 1,2-(*Z*)-disubstituted alkenes.[11a] The extended anthraquinone-1,4-diyl ring in $(DHQD)_2AQN$ is much more bulky than the 1,4-phthalazinediyl skeleton in $(DHQD)_2PHAL$. We were not sure whether the increasing steric demand of the ligand backbone could suppress the undesired dihydroxylation of the C12=C13 double bond in (*E*)-**8** from the direction near to the C14 methyl group or the ligand could favorably promote dihydroxylation of the C16 methylene group in **15b**, leading to better kinetic resolution among the diols **15a** and **15b**.[21] Fortunately, we found that the ratio of **15a**/**15b** could be enhanced to 85:15 with a similar isolated yield of the tetraol **15c** although the lower total mass recovery (70%) was not understood (entry 4 vs. entry 3, Table 2). By reducing the amount of Os to 2.5 mol% with an Os/$(DHQD)_2AQN$ ratio of 1:4, the tetraol **15c** was significantly diminished to 5%, while the diols **15a** and **15b** were isolated in 59 and 13% yields, respectively (entry 5, Table 2). The improved ratio of **15a**/**15b** using $(DHQD)_2AQN$ supports the above-mentioned chirality-matched dihydroxylation of (*E*)-**8** using the hydroquinidine-derived ligands.[21]

We attempted selective AD of (*Z*)-**8** using the hydroquinine-derived ligand, $(DHQ)_2PHAL$, but the result was inferior: the diol **15d** was obtained as a 50:50 mixture of two inseparable diastereomers in 30% combined yield, implying a nonstereoselective dihydroxylation of the C12=C13 endocyclic double bond in (*Z*)-**8** (entry 6, Table 2). Isolation of the diol **15e** (15% yield) suggests that the C12=C13 double bond in **15e** is difficult to undergo further dihydroxylation presumably due to a change in the ring conformation. Improvement on selective AD of (*Z*)-**8** should await for future investigation.

With the diol **15a** in hand, it was smoothly transformed into the target macrolide **2** (Scheme 5). When **15a** was subjected to silylation, only the C12 TBS ether **16** was obtained in 77% yield as the result of steric hindrance around the C13 hydroxy group in **15a** and **16**. Finally, DMP oxidation of **16** followed by global desilylation gave **2** in 87% overall yield. The ^1H and ^{13}C NMR spectroscopy data of our synthetic **2**, with $[\alpha]_D^{27} = -28.6$ ($c = 0.50$, $CHCl_3$), are identical to those of the natural macrolide.[2b]

In conclusion, we have accomplished the first total synthesis of **2** in 8.0% overall yield from methyl (*S*)-lactate through a 16-step sequence, highlighting installation of the C12/C13 "α-hydroxy ketone" subunit by RCM and AD in a regio- and stereoselective manner. Our approach is flexible and might be applicable to the total synthesis of other amphidinolide T congeners. Selective dihydroxylation of the endocyclic (*E*)-1,2-disubstituted double bond over the exocyclic methylene in (*E*)-**8** is interesting and suggests steric hindrance among the substrate and the bulky oxidant as the major factor for the selectivity.[11b]

Acknowledgements

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Keywords: dihydroxylation · macrocycles · metathesis · regioselectivity · total synthesis

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[21] A discussion on AD of (*E*)-**8** and (*Z*)-**8** can be found in the Supporting Information.

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