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Studies toward the total synthesis of armatol F: stereoselective construction of the C6 and C7 stereocenters and formation of the A-ring skeleton

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ABSTRACT

Armatol F, isolated from the red alga *Chondria armata* as a polyether triterpene, has a solitary oxepane (A-ring) and a fused tricyclic ether moiety (BCD-ring). The A-ring features a rare cis-relationship between the hydroxy group at the quaternary carbon C6 and the carbon chain at C7. As part of our program toward the total synthesis of armatol F, a new stereoselective method for the construction of the C6 and C7 stereocenters has been developed based on chirality-transferring Ireland-Claisen rearrangement. The A-ring skeleton has also been synthesized from the rearrangement product by a process including ring-closing olefin metathesis.

Armatol F (**1**, Fig. 1) was isolated from the red alga *Chondria armata* by Ciavatta et al. as a polyether triterpene.[1] It has a solitary oxepane (A-ring), a fused tricyclic ether moiety (BCD-ring), and bromo substituents at both ends of the molecule. Partial relative configurations of the A-ring and the BCD-ring have been determined by NMR analysis, though the relative relationship between the A and the BCD-rings and the configuration at C10 is unclear. The partial absolute stereochemistry of the A-ring can be deduced as shown in Figure 1 by analogy with that of armatol A, a congener of **1**.[1]

It is remarkable that the hydroxy group at the C6 quaternary carbon in the A-ring of **1** is in a cis-relationship to the carbon chain at C7, because the cis-configuration is unusual among the natural oxepanes possessing similar substituents.[2] The cis-fusion between the C and D rings of **1** is also unusual for natural fused polycyclic ethers.[3,4]

The remarkable structural characteristics of **1** prompted us to initiate a program toward the total synthesis and determination of full absolute configuration of **1**. As part of the program, the synthesis of the A-ring has been studied. We describe herein the stereoselective construction of the C6 and C7 stereocenters based on chirality-transferring Ireland-Claisen rearrangement and the formation of the A-ring skeleton.

The outline of the synthesis of the A-ring skeleton (**2**), an important synthetic intermediate for the full functionalized A-ring, is shown in Scheme 1 retrosynthetically. The synthesis included the following challenges: (i) formation of the seven-membered ring of **2** and (ii) stereoselective construction of a congested *tert*-alkoxy β′-methyl-β′-alkoxyalkyl ether, corresponding to the C2–O–C7–C6

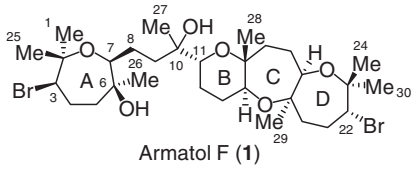
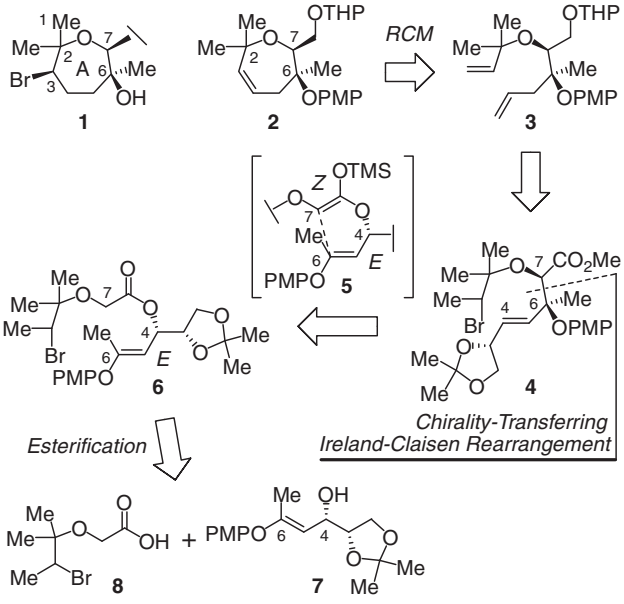


Figure 1.



Scheme 1.

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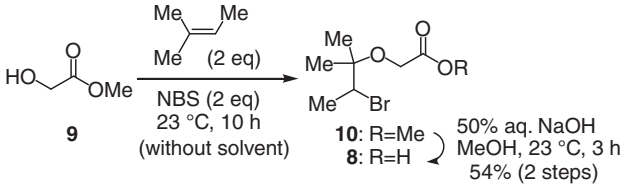
part of **2**. The seven-membered ring was formed by employing the ring-closing olefin metathesis of diene **3**. Applying the Ireland-Claisen rearrangement to ester **6** provided the congested ether **4** in a chirality transferring fashion via a presumed chair-shaped transition state derived from a *Z*-ketene silyl acetal intermediate (**5**).[5,6] The success of the stereoselective rearrangement strongly relied on the stereoselective construction of the substrate's trisubstituted *E*-enol ether group and the adjacent chiral center C4, which originated from alcohol **7**. The counterpart carboxylic acid **8** included a 2-methyl-3-bromo-2-butyl group as a masked 2-methyl-3-buten-2-yl group.

The carboxylic acid **8** was prepared as a racemate by NBS-mediated bromoetherification of 2-methyl-2-butene with methyl glycolate (**9**) without using a solvent and subsequent basic hydrolysis in 54% overall yield based on **9** (Scheme 2).[7]

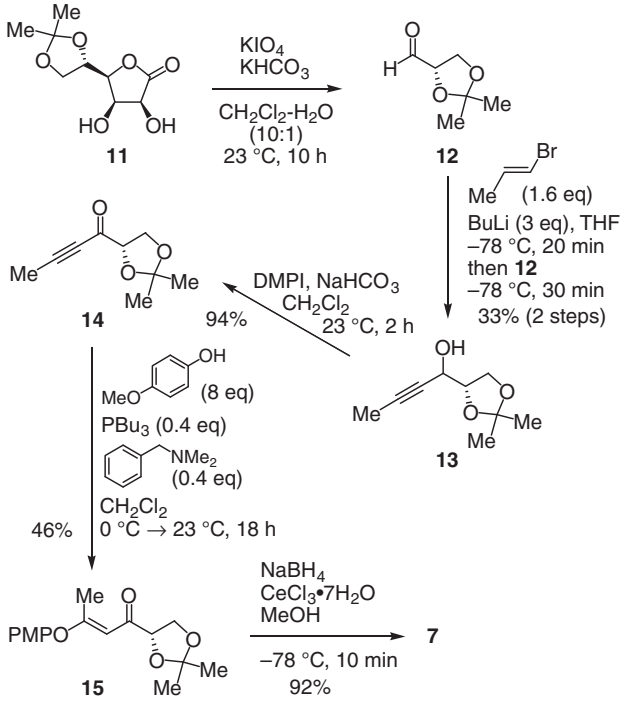
Synthesis of alcohol **7** from 5,6-*O*-isopropylidene-L-gulonic acid γ-lactone (**11**) is shown in Scheme 3.[8] Oxidative cleavage of **11**[9] followed by the addition of propynyl lithium derived from 1-bromo-1-propene gave alcohol **13** as a mixture of diastereomers in 33% overall yield. The alcohol was oxidized with Dess–Martin periodinane to afford acetylene ketone **14** in 94% yield.[10] The hetero-Michael reaction of **14** with an excess amount of 4-methoxyphenol in the presence of PBu_3 and *N*,*N*-dimethylbenzylamine furnished *E*-enol ether ketone **15** as a single geometrical isomer in 46% yield.[11] The absence of PBu_3 or *N*,*N*-dimethylbenzylamine resulted in a poor yield of **15**. The mechanistic details are unknown at present. The diastereoselective reduction of **15**, assisted by the neighboring 2,2-dimethyl-1,3-dioxolan-4-yl group,[12] produced **7** in 92% yield under Luche conditions.[13,14]

The enantiomer of **7** (***ent*-7**) was also prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**16**)[15] in a similar manner (Scheme 4).

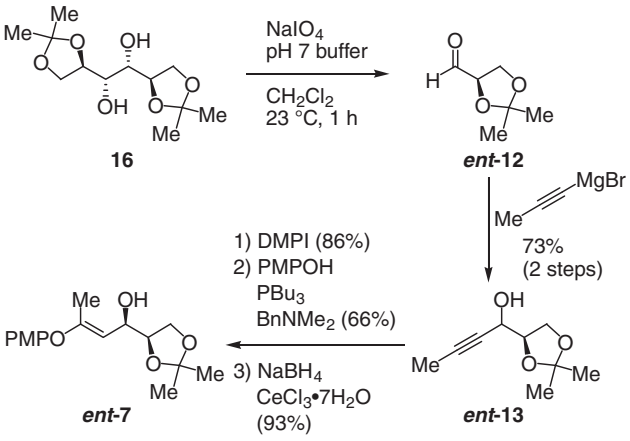
The stereoselective construction of the quaternary and tertiary centers at C6 and C7, respectively, was first examined with ***ent*-7** and **8** (Scheme 5). Esterification of ***ent*-7** with **8**, mediated by EDCI·HCl and DMAP, smoothly produced ester ***ent*-6**, which was subjected to the next reaction immediately after purification because of its instability. The ester was then treated with LDA followed by TMSCl at −78 °C, and the resulting ketene silyl acetal was rearranged by warming to ambient temperature to produce carboxylic acids, which were converted to ***ent*-4** and **17** by methylation with



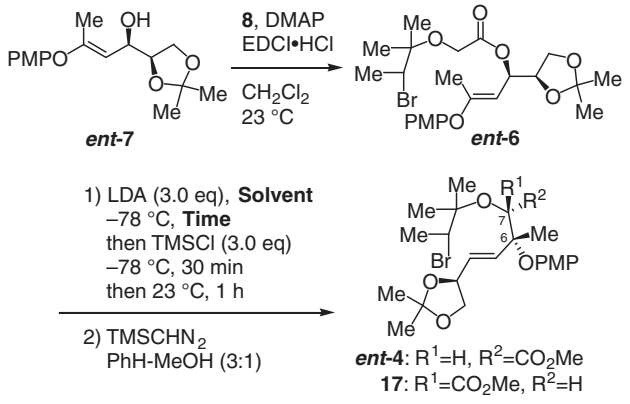
Scheme 2.



Scheme 3.



Scheme 4.



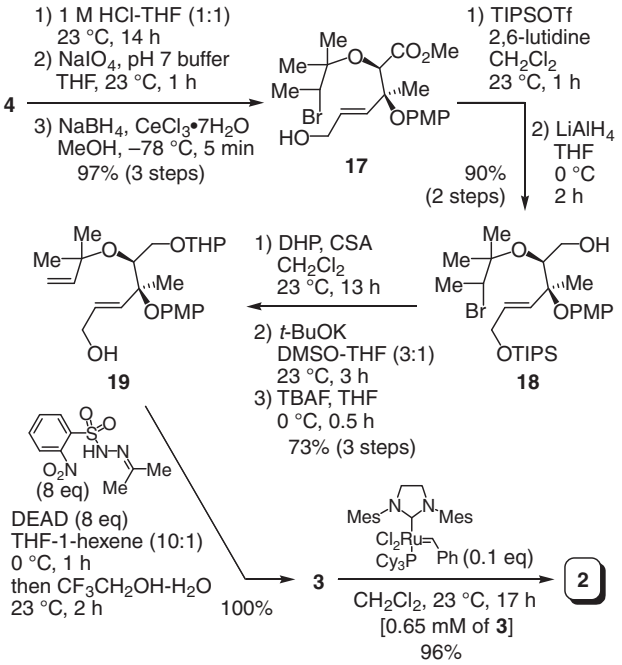
Scheme 5.

Entry	Solvent[a]	Time	Yield (3 steps)	***ent*-4** : **17**
1	THF	20 min	52%	1.4 : 1
2	Et_2O-THF (14:1)	20 min	36%	1.3 : 1
3	toluene-THF (14:1)	20 min	78%	5 : 1
4	toluene	20 min	39%	≥20 : 1
5	toluene	5 min	66%	13 : 1
6[b]	toluene	5 min	52%	**4** : ***ent*-17** = ≥20 : 1

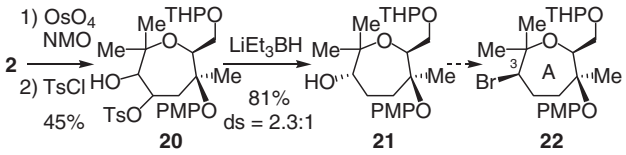
[a] A small amount of hexane (~10%, from BuLi soln.) was contained.
[b] Alcohol **7** was used instead of ***ent*-7**.

TMS-diazomethane. During optimization of reaction conditions to obtain the desired ***ent*-4** exclusively, we observed a significant solvent effect on the selectivity of ***ent*-4** and **17**, shown in the inset table in Scheme 5.[16] When THF or Et_2O was used as solvent, the ratio of ***ent*-4** to **17** was low (1.3–1.4:1) (entries 1 and 2). Treatment of a solution of ester ***ent*-6** in toluene with a solution of LDA in THF enhanced the combined yield (78% over three steps) and the ratio of ***ent*-4** (5:1) (entry 3). Exclusion of THF from the reaction media by use of a solution of LDA in toluene produced ***ent*-4** predominantly ($\geqslant$20:1), but in moderate yield (39% over three steps) (entry 4). Since the decreased yield was attributable to the instability of an enolate intermediate from ***ent*-6** in toluene, the time period for deprotonation from the substrate was shortened to avoid decomposition of the enolate. As a result, a 5-min treatment of ***ent*-6** with LDA effectively furnished ***ent*-4** in good yield (66% over three steps) with high selectivity (13:1) (entry 5).[19] The optimized conditions were applied to natural enantiomer **7**, and the desired **4**[20] was obtained exclusively in 52% yield over three steps. Thus, the stereoselective construction of the quaternary and tertiary stereocenters at C6 and C7, respectively, of the A-ring of **1** was achieved.

The construction of the seven-membered ring from **4** is illustrated in Scheme 6. The 2,2-dimethyl-1,3-dioxolan-4-yl group of **4** was transformed to a hydroxymethyl group via acidic hydrolysis, oxidative diol cleavage, and Luche reduction (97% over three steps). The protection of the resulting **17** as a TIPS ether followed by reduction of the ester group afforded alcohol **18** (90% over two steps). After THP protection of **18**, the resulting THP ether was treated with *t*-BuOK in a 3:1 DMSO–THF solution to give a mixture of a dehydrobrominated product and its desilylated alcohol (**19**).[7] Complete desilylation of the mixture with TBAF provided **19** in good overall yield (73% over three steps). The allyl alcohol group of **19** was then converted to a terminal alkenyl group according to Movassaghi's procedure.[21] Substitution of the hydroxyl group of **19** with *N*-isopropylidene-*N*′-(2-nitrophenylsulfonyl)hydrazide (IPNBSH) under Mitsunobu conditions[22] in the presence of an excess amount of 1-hexene as a scavenger of free diimide,[6c] followed by in situ hydrolysis of the hydrazone group, induced spontaneous elimination of a sulfinate and reductive olefin migration to produce diene **3** quantitatively. Ring-closing olefin



Scheme 6.



Scheme 7.

metathesis of **3** in the presence of second-generation Grubbs' catalyst[23] smoothly furnished **2**[24,20] in excellent yield (96%), thereby completing the stereoselective construction of the A-ring skeleton of **1**. Similarly, the enantiomer of **2** (***ent*-2**) was synthesized from ***ent*-4** (overall 54%). Both **2** and ***ent*-2** would be available for the synthesis of **1** and its stereoisomers aiming at determination of full absolute stereochemistry.

In conclusion, the A-ring skeleton (**2**) of armatol F (**1**), which has unique configurations at C6 and C7 among natural oxepanes, has been constructed based on chirality-transferring Ireland-Claisen rearrangement and ring-closing olefin metathesis. Transformation of **2** to the full functionalized A-ring (**22**) is currently underway via a route including dihydroxylation, selective tosylation, reduction by Robins' procedure,[25] and installation of a bromo group (Scheme 7). At present, alcohol **21** was obtained stereoselectively as a preliminary result.[26] Further studies toward the total synthesis of armatol F are in progress in this laboratory, specifically the stereoselective installation of a bromo group at C3 in the A-ring and the construction of the BCD-ring.

Acknowledgments

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20. The absolute configuration at C7 was determined by applying the modified Mosher's method to an alcohol derived from **18** via acetylation followed by reductive elimination of the 3-bromo-2-methyl-2-butyl group with Zn/AcOH. The absolute configuration at C6 was elucidated from the cis-relationship between H7 and 6-CH_3 of **2**. The cis-relationship was confirmed by the presence of a clear NOE between H7 and 6-CH_3 of an alcohol derived from **2** via removal of the THP group. For modified Mosher's method, see: Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
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24. *Selected spectral data of* **2**: a 1:1 mixture of epimers at the acetal carbon of the THP group; a colorless oil; $[\alpha]_D^{26}$ −5.4 (*c* 0.37, $CHCl_3$); IR (neat) *ν* 3020, 2971, 2936, 2866, 1504, 1216, 1121, 1096, 1031, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 1.25 (3H, s), 1.27 (1/2 × 3H, s), 1.30 (1/2 × 3H, s), 1.41 (3H, s), 1.49–1.89 (6H, m), 3.12–3.21 (1H, m), 3.48–3.56 (1H, m), 3.67 (1/2 × 1H, dd, *J* = 8.8, 11.3 Hz), 3.73–3.77 (1/2 × 1H, m), 3.76 (3H, s), 3.84–4.01 (1/2 × 1 + 2H, m), 4.11 (1/2 × 1H, dd, *J* = 2.0, 11.5 Hz), 4.67 (1/2 × 1H, br dd, *J* = 2.4, 4.6 Hz), 4.73 (1/2 × 1H, br t, *J* = 2.9 Hz), 5.36 (1H, br d, *J* = 10.8 Hz), 5.42–5.51 (1H, m), 6.76 (2H, br d, *J* = 9.2 Hz), 6.94 (2H, br d, *J* = 9.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 18.8 (1/2 × CH_2), 19.9 (1/2 × CH_2), 22.8 (CH_3), 25.5 (CH_2), 26.1 (1/2 × CH_3), 26.2 (1/2 × CH_3), 28.8 (CH_3), 30.5 (1/2 × CH_2), 30.7 (1/2 × CH_2), 34.7 (1/2 × CH_2), 34.8 (1/2 × CH_2), 55.5 (CH_3), 61.0 (1/2 × CH_2), 62.6 (1/2 × CH_2), 66.8 (1/2 × CH_2), 67.8 (1/2 × CH_2), 78.1 (1/2 × CH), 79.1 (C), 79.2 (1/2 × CH), 84.5 (C), 97.2 (1/2 × CH), 100.0 (1/2 × CH), 113.8 (2 × CH), 122.39 (1/2 × CH), 122.44 (1/2 × CH), 124.7 (2 × CH), 138.5 (CH), 148.3 (1/2 × C), 148.4 (1/2 × C), 155.5 (C); LR-EIMS *m/z* 376 (23.5%, $[M^+]$), 124 (bp, $[PMPOH^+]$); HR-EIMS calcd for $C_{22}H_{32}O_5$ $[M^+]$: 376.2250, found: 376.2245. Selected spectral data of an alcohol derived from **2** via removal of the THP group: a colorless oil; $[\alpha]_D^{25}$ −4.9 (*c* 0.19, $CHCl_3$); IR (neat) *ν* 3468, 3020, 2971, 2928, 2854, 1505, 1464, 1374, 1214, 1182, 1135, 1093, 1036, 839 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) *δ* 1.09 (3H, s), 1.11 (3H, s), 1.32 (1H, br s), 1.36 (3H, s), 1.59 (1H, dd, *J* = 8.8, 12.0 Hz), 3.24 (1H, br dd, *J* = 5.2, 12.0 Hz), 3.30 (3H, s), 3.75 (1H, dd, *J* = 3.6, 8.4 Hz), 3.99 (1H, dd, *J* = 3.6, 12.0 Hz), 4.13 (1H, dd, *J* = 8.4, 12.0 Hz), 5.06 (1H, dd, *J* = 2.4, 10.8 Hz), 5.11 (1H, ddd, *J* = 5.2, 8.8, 10.8 Hz), 6.70 (2H, br d, *J* = 9.2 Hz), 6.92 (2H, br d, *J* = 9.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 23.0 (CH_3), 26.5 (CH_3), 28.8 (CH_3), 34.7 (CH_2), 55.5 (CH_3), 62.5 (CH_2), 79.3 (C), 79.6 (CH), 84.7 (C), 113.9 (2 × CH), 122.7 (CH), 124.7 (2 × CH), 137.9 (C), 148.0 (C), 155.8 (C); LR-EIMS *m/z* 292 (5.2%, $[M^+]$), 124 (bp, $[PMPOH^+]$); HR-EIMS calcd for $C_{17}H_{24}O_4$ $[M^+]$: 292.1674, found: 292.1668.
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