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Model studies for the stereoselective construction of the BC-ring of armatol F based on Ireland-Claisen rearrangement and relay ring-closing olefin metathesis

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ABSTRACT

Armatol F, isolated from the red alga *Chondria armata* as a polyether triterpene, has a fused tricyclic ether moiety (BCD-ring) with an unusual *cis* ring junction at C18–C19 between the C- and D-rings. En route to the total synthesis of armatol F, the stereoselective construction of the C18 and C19 stereocenters by Ireland-Claisen rearrangement and the formation of the C-ring by relay ring-closing olefin metathesis were established through the synthesis of monocyclic (C-ring) and bicyclic (BC-ring) model compounds.

Armatol F (**1**, Fig. 1), isolated from the red alga *Chondria armata* by Ciavatta et al. as a polyether triterpene, is characterized by a solitary oxepane (A-ring), a fused tricyclic ether moiety (BCD-ring), and two bromo substituents at opposite ends of the molecule.[1] The cis ring fusion at C18–C19 between the C- and D-rings of **1** is unusual for naturally occurring fused polycyclic ethers.[2,3] Although the respective partial relative configurations of the A- and the BCD-rings have been determined by NMR experiments, the full absolute stereochemistry of **1** remains unclear. Since the unusual structure of **1** has attracted our interest, we started a program toward the total synthesis and determination of full absolute configuration of **1**.[4] As a part of this program, the synthesis of the BCD-ring has been studied. Herein, the stereoselective construction of the stereocenters at C18 and C19 by Ireland-Claisen rearrangement[5,6] and the formation of the C-ring by relay ring-closing olefin metathesis,[7] both of which were established through the synthesis of C-ring model **2** and BC-ring model **3**, are described.

The outline of the synthesis of C-ring model **2** and 15-Me-omitted BC-ring model **3** is shown in Scheme 1 retrosynthetically. The seven-membered ring (C-ring) formation, employing ring-closing olefin metathesis (RCM) or relay RCM, was undertaken at the final stage of the synthesis. The stereoselective construction of the contiguous trisubstituted C18 and tetrasubstituted C19 stereocenters of **4** and **5** relied on the Ireland-Claisen rearrangement of an *E*-3-alkoxy-2-propenyl lactate (**7** and **8**), of which the chirality at C16' was transferred to C18 and C19 of the product (**4** and **5**) via a presumed chair form transition state derived from a *Z*-ketene silyl acetal intermediate (**6**). Lactate esters **7a,b** and **8a,b** were prepared from alcohol **11** and lactic acid derivatives **9a,b** and **10a,b**.

Alcohol **11** was prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**12**) (Scheme 2).[8] Oxidative cleavage of **12** with $NaIO_4$,[9] followed by the reaction with ethynyl magnesium bromide, produced **14** (60% over two steps), which was oxidized with IBX[10] in refluxing ethyl acetate to give **15**.[11] Conjugate addition of 4-methoxybenzyl alcohol to **15** in the presence of PMe_3 selectively afforded *E*-enone **16** (51% over two steps).[12] The enone was diastereoselectively reduced to **11**[13] (ds >7:1, 93%) under Luche conditions[14] by the assistance of the neighboring chiral 2,2-dimethyl-1,3-dioxolan-4-yl group.[15]

Simple lactic acids **9a** and **9b** were synthesized from *R*- and *S*-2-bromopropionic acids (**18**), respectively, by substitution with **17** under basic conditions without the loss of optical purity (**9a**: 73%; **9b**: 65%) (Scheme 3).[16] The optical purities of **9a** and **9b** were determined by NMR analysis of **19a** and **19b** derived from **9a** and **9b** with *S*-1-phenylethylamine. The absolute configurations of **9a** and **9b** were confirmed by the X-ray crystallographic analysis of **19b**.[17]

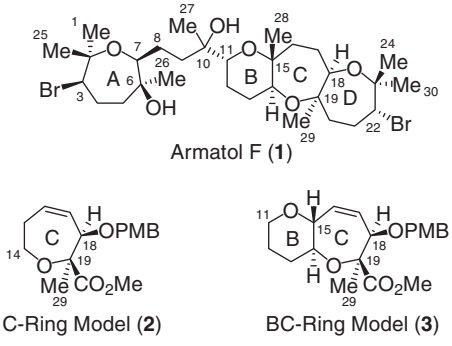

Figure 1.

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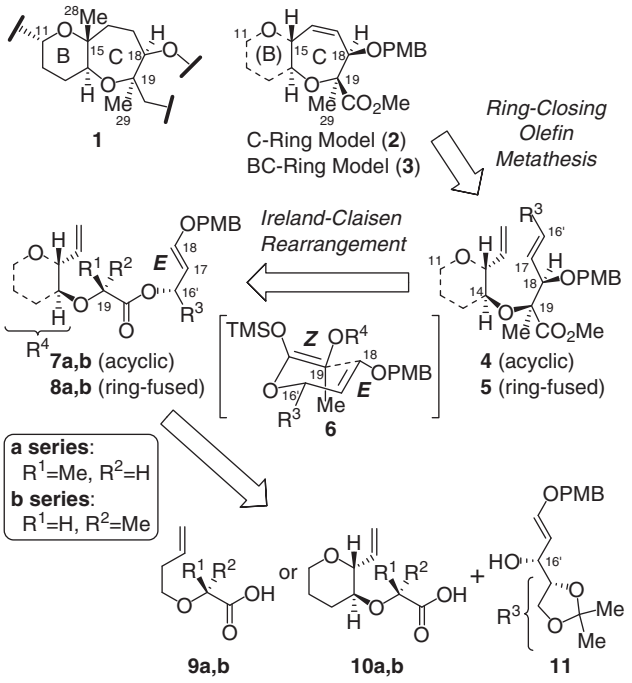
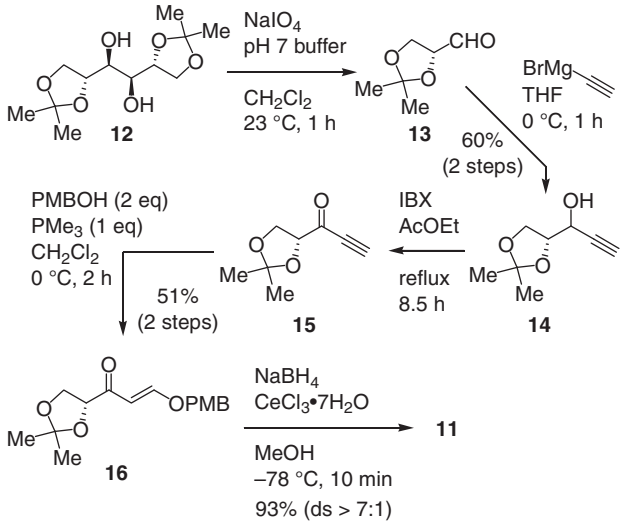


Scheme 1.

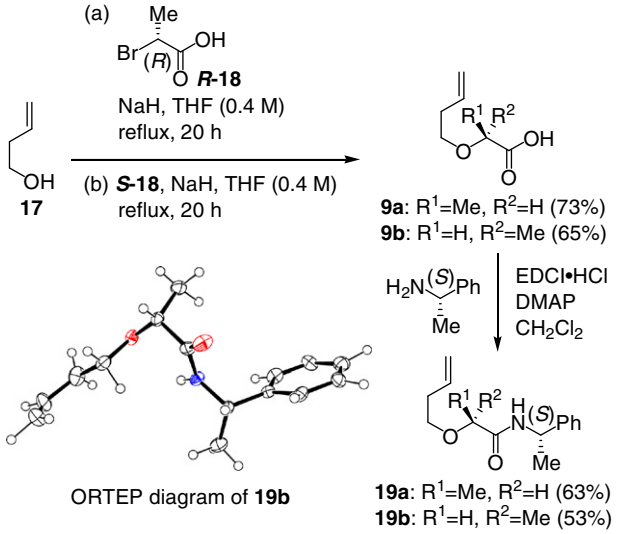


Scheme 2.

Similarly, lactic acids **10a** and **10b** were prepared from ***R***- and ***S*-18**, respectively, by the reaction with known **20**,[18] derived from tri-*O*-acetyl-D-glucal (**10a**: 53%; **10b**: 69%) (Scheme 4).[16] The stereochemistry at C19 of **10a** and **10b** was determined by NMR analysis of lactone **23a**, derived from **10a** through a five-step process [(i) esterification, (ii) dihydroxylation/oxidative cleavage, (iii) reduction, (iv) hydrolysis, and (v) lactonization]. The presence of an NOE between H14 and 19-CH_3 of **23a** indicated the *S* configuration at C19 of **10a**.

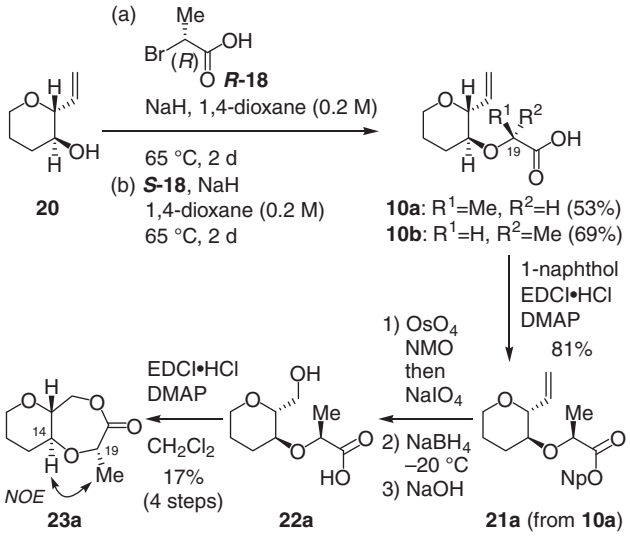
Alcohol **11** was esterified with **9a,b** and **10a,b** using EDCI·HCl and DMAP to afford **7a,b** (as crude products) and **8a,b** (89% and 97%), respectively (Scheme 5). Since simple esters **7a** and **7b** were unstable, contrary to **8a** and **8b**, they were immediately used in the next reaction without further purification.

Selected results of the Ireland-Claisen rearrangement of **7a,b** and **8a,b** are shown in Scheme 6. Each ester was treated with

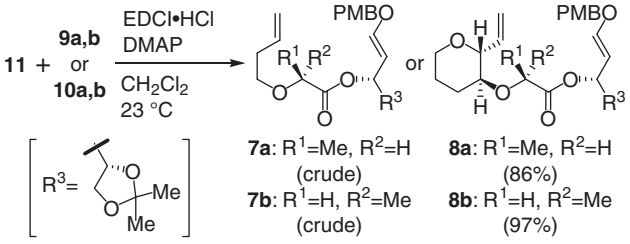


Scheme 3.

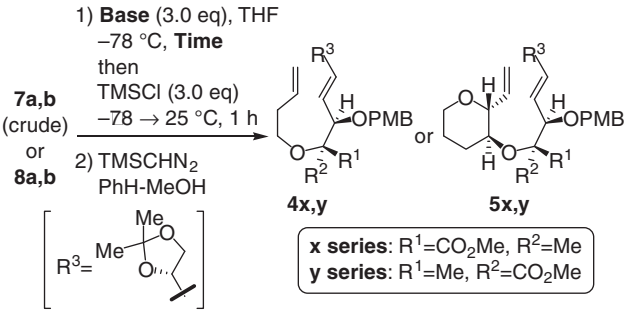
LDA or KHMDS in THF at −78 °C for 10 or 30 min and then with TMSCl at −78 °C, and the resulting ketene silyl acetal was rearranged by warming to ambient temperature to produce carboxylic acids, which were converted to **4x,y** or **5x,y** by methylation with TMS-diazomethane. In the case of **7a** and **7b**, both LDA and KHMDS produced desired **4x** as a major product along with **4y** (entries 1–8). Increasing time of LDA exposure did not affect the selectivity of **4x** but slightly decreased the yield (entries 1, 2, 5, and 6). Although the treatment of **7a** with KHMDS showed a good ratio of **4x** (>20–



Scheme 4.



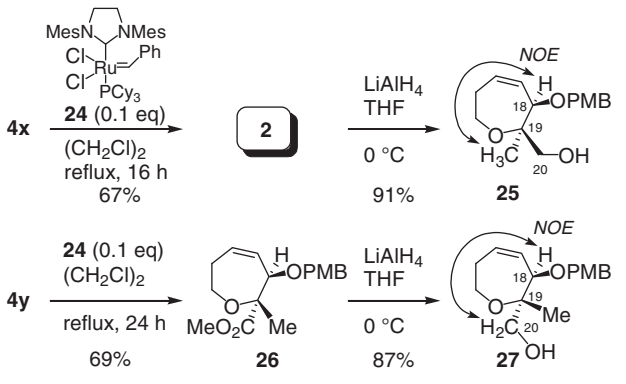
Scheme 5.



Entry	Substrate	Base	Time	Products 4/5	Yield (x+y)	x : y
1		LDA	10 min	**4**	74%[a]	3 : 1
2		LDA	30 min		67%[a]	3 : 1
3		KHMDS	10 min		53%[a]	9 : 1
4	**7a**	KHMDS	30 min		16%[a]	>20 : 1
5		LDA	10 min	**4**	74%[a]	4 : 1
6		LDA	30 min		57%[a]	4 : 1
7		KHMDS	10 min		58%[a]	3 : 1
8	**7b**	KHMDS	30 min		Dec[b]	ND[b]
9		LDA	10 min	**5**	59%[c]	1 : 4
10		LDA	30 min		35%[c]	1 : 4
11		KHMDS	10 min		NR[b]	ND[b]
12	**8a**	KHMDS	30 min		NR[b]	ND[b]
13		LDA	10 min	**5**	66%[c]	1 : 4
14		LDA	30 min		62%[c]	1 : 4
15		KHMDS	10 min		53%[c]	9 : 1
16	**8b**	KHMDS	30 min		26%[c]	16 : 1

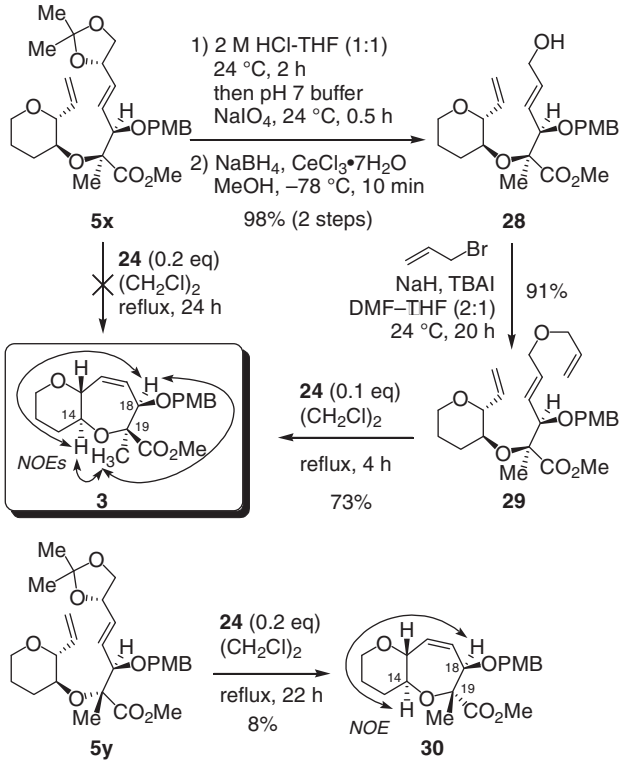
[a] a three-step yield from **11**. [b] Dec: decomposition; NR: no reaction (recovery of substrate); ND: not determined. [c] a two-step yield from **8**.

Scheme 6.



Scheme 7.

9:1), longer treatment of **7a** or **7b** with KHMDS decomposed the substrate and decreased the yield (entries 3, 4, 7 and 8). It is notable that the LDA-promoted rearrangement of **8a** and **8b** afforded undesired **5y** as a major product (entries 9, 10, 13, and 14), contrary to the results from **7a** and **7b**. Interestingly, KHMDS was effective for **8b** to produce desired **5x** with good selectively (16–9:1) but was unproductive for **8a** (entries 11, 12, 15, and 16). It was also observed that the yield from **8b** decreased with increasing time of KHMDS exposure (entry 16). Although significant dependence of reactivity/stereoselectivity on the substrate structure was observed, the Ireland-Claisen rearrangement producing the required stereochemistry at C18 and C19 for **1** was thus optimized by applying the 10-min treatment with KHMDS to the 19*R*-lactate substrate.



Scheme 8.

The cyclization of **4x** and **4y** by RCM with second-generation Grubbs' catalyst (**24**)[19] in refluxing 1,2-dichloroethane smoothly produced C-ring model **2** (67%) and **26** (69%), respectively (Scheme 7). The full absolute configurations of **2** and **26** as well as **4x** and **4y** were elucidated by observation of NOE correlations in alcohols **25** (H18/19-CH_3) and **27** (H18/H20), derived, respectively, from **2** and **26**, and by application of the modified Mosher's method[20] to alcohols derived from **25** and **27** via TBS-protection and PMB-detachment.

The attempt to cyclize **5x** to BC-ring model **3** by RCM with **24** was unsuccessful (86% recovery of **5x**), and the RCM of **5y** only resulted in a low yield of 19-*epi*-BC-ring model **30** (8%) (Scheme 8). These results might be attributable to the steric congestion around the double bond at C17. Therefore, the conversion of **5x** to **3** employed a process including the removal of the bulky 2,2-dimethyl-1,3-dioxolan-4-yl group and relay RCM, which was reported to be effective for preparing sterically hindered cyclic alkenes.[7] Thus, one-pot acidic hydrolysis/oxidative diol cleavage, followed by Luche reduction,[14] transformed **5x** to allyl alcohol **28** (overall 98%), which was reacted with allyl bromide to afford **29** (87%). Upon treatment with a catalytic amount of **24** in refluxing 1,2-dichloroethane, diallyl ether **29** was successfully cyclized to BC-ring model **3** (73%). The stereochemistry of **3** and **30** was determined by the NOE correlations shown in Scheme 8 (**3**: H18/19-CH_3, H14/19-CH_3, H14/H18; **30**: H14/H18), thereby also confirming the stereochemistry of rearrangement products **5x** and **5y**.

In conclusion, in our studies toward the total synthesis of armatol F (**1**), a synthetic route including the stereoselective construction of the C18 and C19 stereocenters by Ireland-Claisen rearrangement and the formation of the C-ring by relay RCM was established through the synthesis of C-ring model **2** and

15-Me-omitted BC-ring model **3**. Further studies toward the total synthesis of **1** are currently in progress.

Acknowledgments

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Supplementary data

Supplementary data associated (spectral data of **2**, **25**–**27**, **3**, and **30**) with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.103.

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17. Crystal data of **19b**: $C_{15}H_{21}NO_2$, M 771.74, orthorhombic $P2_12_12_1$ (No. 19), a = 5.306(1) Å, b = 15.353(3) Å, c = 16.913(4) Å, V = 1377.8(5) Å^3, D_c (Z = 4) = 1.192 g/cm^3, T = 153 K, μ = 0.78 cm^{-1}. The final R value is 0.077 for 1745 independent reflections with $I > 2\sigma I$ and 163 parameters. Crystallographic data (excluding structure factors) of **19b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 776515. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]
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