Natural Products Synthesis

Total Synthesis of Natural Myriaporones

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Myriaporones 1–4 (**1**–**4**, respectively) are a new class of cytotoxic marine polyketide-derived compounds that exhibit significant cytotoxic activity against L1210 cells. These compounds **1**–**4** were isolated by Rinehart and co-workers in 1995 from the bryozoan *Myriapora truncata*.[1] The most active constituents, **3** and **4**, were isolated as a mixture of cyclic and open-chain isomers. The myriaporones are structurally related to the C10–C23 region of the macrocycles tedanolide (**5**)[2] and deoxytedanolide (**6**),[3,4] although the configuration at C5 of **1** and **2** and at C5 and C6 of **3** and **4** were not unequivocally determined. Additionally, the absolute configuration of the myriaporones was unknown. The functionality that flanks the C7 carbonyl group confers significant lability to the myriaporones, which makes these densely functionalized structures challenging synthetic targets.

Taylor et al. described progress toward the preparation of myriaporone 1 (**1**) by a strategy based on an homoallenylboration and a nitrile oxide cycloaddition.[5] Furthermore, Yonemitsu and co-workers reported the synthesis of advanced intermediates from D-glucose.[6] On the other

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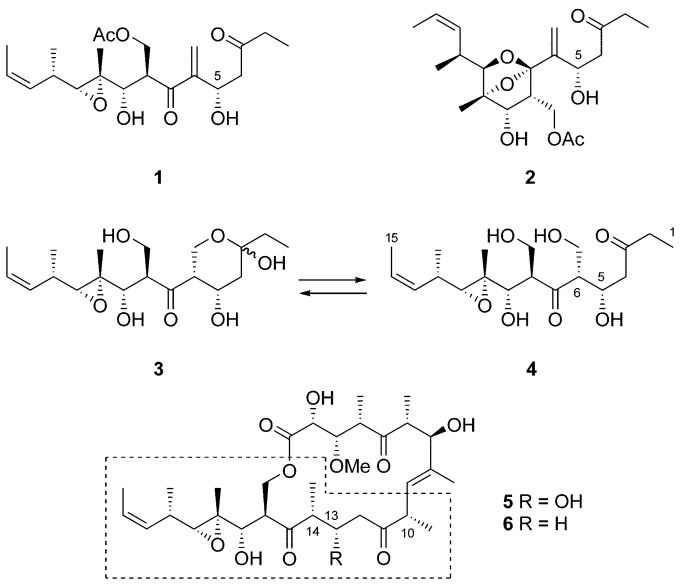
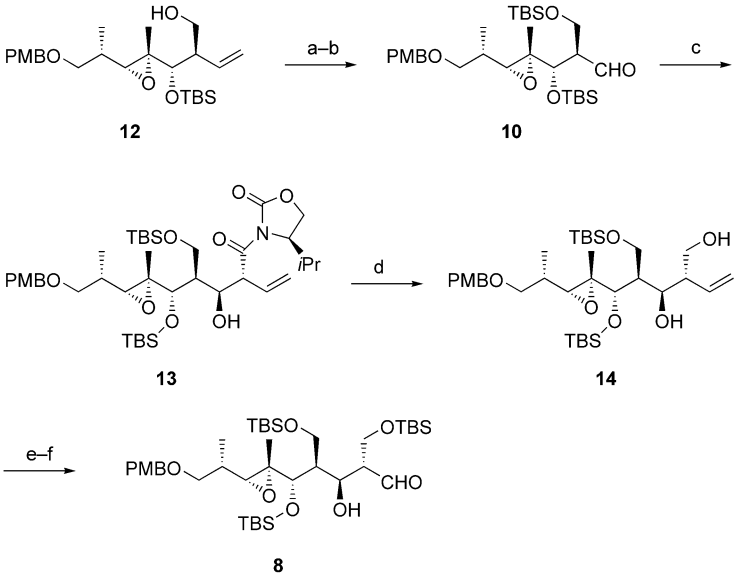


hand, several syntheses of the C10–C23 region of **5** and **6** have been described[4,7–9] as part of synthetic efforts directed towards the total synthesis of the macrolides. However, a total synthesis of any member of the myriaporone family has not yet been described. Herein we report the total synthesis of myriaporones **1**, **3**–**4**, which allowed the confirmation of their structure and the determination of the absolute configuration.

Our retrosynthetic approach to the myriaporones is outlined in Scheme 1, and was based on the assumption that the configurations of C5 and C6 were identical to those of tedanolide (**5**). We planned to introduce the ethyl side chain and the *Z* alkene from Weinreb amide **7**, itself available by an aldol reaction of **8** with acetamide **9**. For the key stereoselective C–C formation, we relied on an Evans aldol reaction[10] between aldehyde **10** and chiral oxazolidinone **11**.[11] To avoid epimerization, as well as retro-aldol and elimination reactions, oxidation to the keto group at C7 was postponed until the final steps of the synthesis.

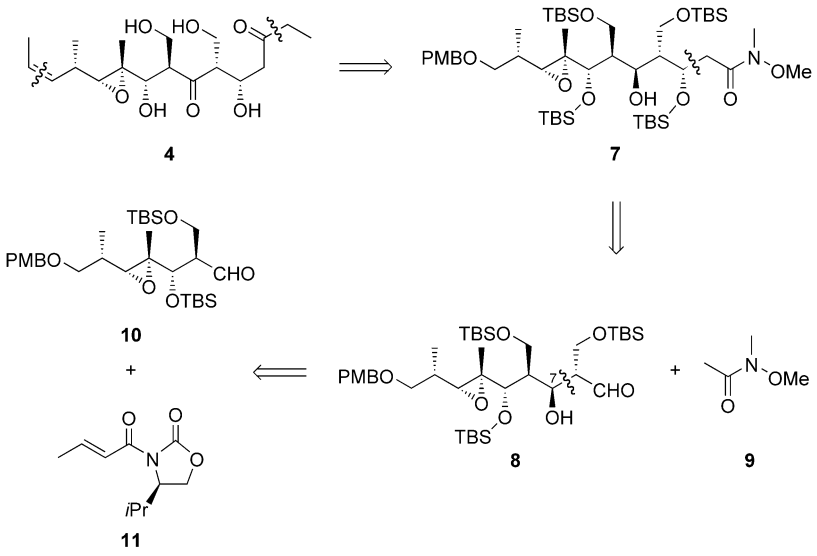
Aldehyde **10** was prepared from **12**, readily available in nine steps from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate by the procedure described by Roush and Lane.[7] Protection of the primary alcohol of **12** as the TBS ether and oxidative cleavage of the olefin furnished aldehyde **10** (Scheme 2). Reaction of the boron enolate of chiral crotonate



Scheme 2. a) TBSCl, imidazole, CH_2Cl_2, 23 °C, 90%; b) O_3, CH_2Cl_2; Ph_3P, −78 °C, 70%; c) (*R*)-**11**, *n*Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; **10**, CH_2Cl_2, −30 °C, 90%; d) $LiBH_4$, THF/H_2O, 0→23 °C; H_2O_2, Et_2O, 0 °C, 95%; e) TBSCl, imidazole, CH_2Cl_2, 23 °C, 92%; f) O_3, CH_2Cl_2; Ph_3P, −78 °C, 82%. Tf = trifluoromethanesulfonyl.

imide (*R*)-**11**[11] with **10** furnished aldol **13** with excellent stereoselectivity (> 99:1).[10] Although the secondary alcohol generated in the aldol reaction will ultimately be oxidized to a ketone, we found that the aldol product with the opposite configuration at C7 (myriaporone numbering) rearranged quantitatively under acidic conditions to the corresponding tetrahydrofuran derivative through an intramolecular epoxide-opening reaction. Reduction of the acyl oxazolidinone with $LiBH_4$[12] gave **14**, whose primary alcohol group was protected as a TBS ether. Oxidative cleavage of the terminal double bond provided **8**, the central core of the myriaporones, in good overall yield (41% from **12**, six steps).

Although pure aldehyde **8** can be stored at −30 °C for several months, an intramolecular epoxide-opening reaction[13] occurs quantitatively under acidic conditions at room temperature to give tetrahydrofuran **15** (Scheme 3). A similar cyclization of **14**, followed by the formation of the *p*-methoxybenzylidene derivative, gave tetrahydrofuran

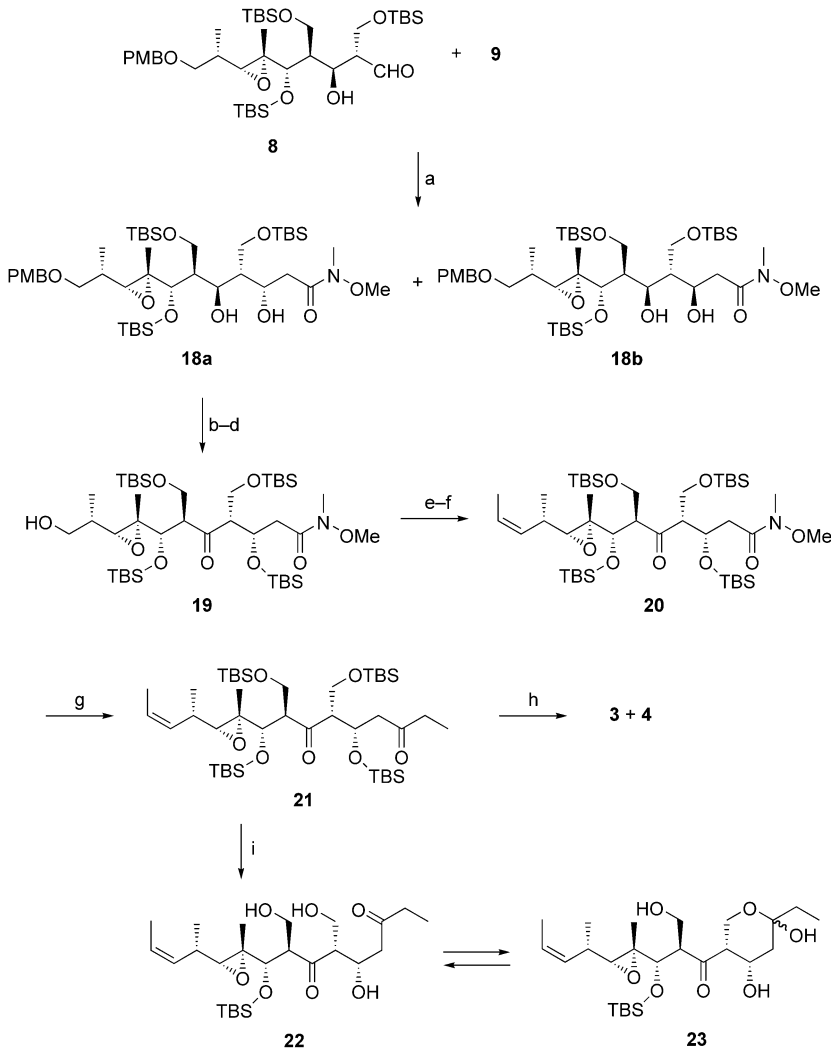


Scheme 1. Retrosynthetic analysis for the synthesis of myriaporone 4 (**4**). TBS = *tert*-butyldimethylsilyl, PMB = *p*-methoxybenzyl.

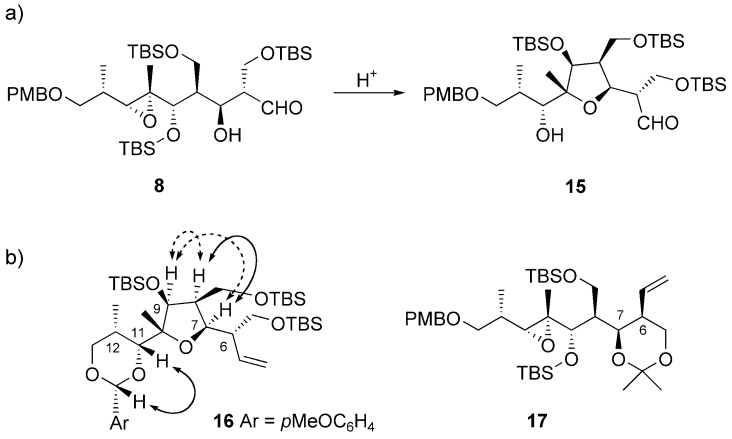
16. Analysis of ^1H–^1H coupling constants and NOESY correlations of **16** allowed the assignment of the configurations of C8–C12 of **8**. A relative *anti* configuration at C6–C7 was determined from the small value of the coupling constant ($J_{H6,H7} = 1.2$ Hz) observed in acetonide **17**, prepared from **14** (Scheme 3).

For the next stage, the aldol reaction between aldehyde **8** and Weinreb acetamide **9** proceed readily in the presence of LDA as base to give **18a** and **18b**[14] in good yield but low stereoselectivity (1:2.5), which were chromatographically separated (Scheme 4). The use of lithium hexamethyldisilazide provided **18a** and **18b** in a 1:3 ratio, whereas the sodium or potassium enolates of **9** furnished almost exclusively *anti*-**18b**. The latter could be partially recycled to **18a** by oxidation of the secondary alcohol with Dess–Martin periodinane[15] followed by reduction of the resulting ketone with $NaBH_4$ in MeOH to afford **18a** and **18b** in a 1:1 ratio (62% yield, two steps).

Selective protection of the less-hindered secondary alcohol of **18a** with TBSOTf and lutidine, followed by oxidation of the alcohol at C7 with DMP and oxidative removal of the PMB group gave **19** (Scheme 4). Based on literature precedent,[4,5] the *Z* olefin was constructed by oxidation with DMP followed by Wittig ethylidenation of the resulting aldehyde to give **20**. Chemoselective addition of ethylmagnesium bromide to the Weinreb amide of **20** afforded ethyl ketone **21**[16] in satisfactory yield on a gram scale. Deprotection of the silyl ethers of **21** with TBAF led to decomposition. However, the use of



Scheme 4. a) **9** + LDA, THF, −78 °C, 91%, **18a,b** (1:2.5); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 81%; c) DMP, CH_2Cl_2, 23 °C; d) DDQ, THF/H_2O, 23 °C, 51%, two steps; e) DMP, CH_2Cl_2, 23 °C; f) $Ph_3PCH_2CH_3Br$, K*t*BuO, toluene, −78 °C, 60%, two steps; g) EtMgBr, THF, 23 °C, 68%; h) TBAF, HOAc, DMF, 23 °C, 35%; i) TBAF, HOAc, THF, 23 °C, 80%. LDA = lithium diisopropylamide; DMP = Dess–Martin periodinane; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; TBAF = tetra-*n*-butylammonium fluoride.

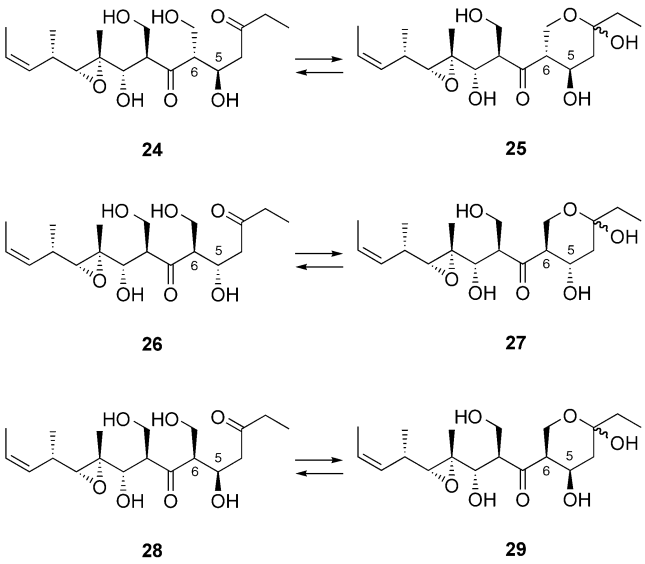


Scheme 3. a) Acid-catalyzed cyclization of epoxyaldehyde **8**. b) Derivatives **16** and **17** prepared from alcohol **14** for the determination of the relative configurations. The arrows indicate NOE correlations.

TBAF and HOAc in THF led to the selective removal of three of the protecting groups to give a mixture of **22** and **23** in good yield. Global deprotection of **21** with TBAF and HOAc in DMF gave myriaporones **3**,**4** (1:1). The myriaporones **3**,**4** in CD_3OD were identical in all respects (^1H and ^{13}C NMR, HRMS, HPLC, and TLC) to an authentic sample, which allowed the assignment of their relative configurations as those shown. The cytotoxic activity of synthetic and natural myriaporones **3**–**4** was found to be the same. The myriaporones **3**–**4** undergo partial dehydration on silica gel. Accordingly, acetylation (Ac_2O, Et_3N, $CHCl_3$) of the crude dehydration products obtained after column chromatography gave **1** (30% yield over two steps).

The C5 epimers **24**–**25** of **3**–**4** were also prepared from **18b** by the same reaction sequence.[17] Similarly, the aldol reaction of **10** and the boron enolate of imide (*S*)-**11** led to the series with the non-natural configuration at C6 or C5–C6

(Scheme 5, **26**–**29**).[17,18] The NMR spectra of compounds **24**–**29** were clearly distinct from those of the natural myriaporones **3**–**4**.



Scheme 5. The C5 epimers **24** and **25** of **4** and **3**, respectively, as well the series with the non-natural configuration at C6 or C5–C6, **26**–**29** (see the Supporting Information for details on the synthesis).

In summary, the total synthesis of the myriaporones 1, 3, and 4 (**1**, **3**–**4**) was based on two consecutive aldol reactions.[19] The ethyl ketone was introduced in a straightforward manner by the addition of an ethyl Grignard reagent to the highly functionalized Weinreb amide **20** bearing keto and epoxide functions. The simplicity of this approach is promising for the preparation of new derivatives from this key intermediate. Additionally, this route allows the synthesis of a variety of stereoisomers of **1**, **3**–**4** and other derivatives for further biological testing. This work allowed the unambiguous determination of the relative and absolute configurations of these cytotoxic compounds to be those shown in formulae **1**, **3**–**4**.

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Keywords: aldol reaction · antitumor agents · diastereoselectivity · natural products · total synthesis

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[13] See reference [9] for a similar transformation.

[14] The configuration of the aldol products was assigned by conversion of the 1,3-diols into the corresponding acetonides. The acetonide *of syn*-1,3-diol **18b** gave rise to a signal for the axial methyl group at $\delta = 20.2$ ppm and for the equatorial methyl group at $\delta = 30.0$ ppm in the ^{13}C NMR spectrum, whereas the acetonide of *anti*-1,3-diol **18a** showed the methyl groups at $\delta =$ 24.4 and 25.2 ppm. See: S. D. Rychnovsky, B. Rogers, G. Yang, *J. Org. Chem.* **1993**, *58*, 3511–3515.

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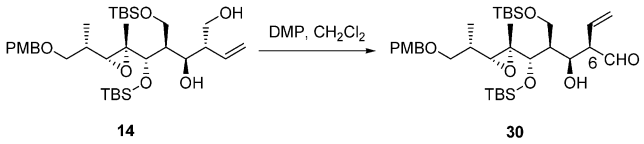
[17] Reaction conditions and yields are given in the Supporting Information.

[18] These series with the non-natural configuration at C6, could also be synthesized from **30**, which was prepared by oxidation of **14**. Further elaboration, as shown in Scheme 4, included the cleavage of the vinyl group by ozonolysis, followed by reduction in situ with $NaBH_4$ to form the alcohol.



[19] For an alternative total synthesis of myriaporones 1, 3, and 4 see following Communication in this issue: K. N. Fleming, R. E. Taylor, *Angew. Chem.* **2004**, *116*, 1760–1762; *Angew. Chem. Int. Ed.* **2004**, *43*, 1728–1730.

