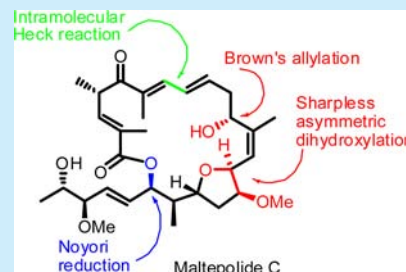


Total Synthesis of the Proposed Structure of Maltepolide C

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S Supporting Information

ABSTRACT: The first total synthesis of the proposed structure of cytotoxic macrolide maltepolide C has been achieved via an *E*-selective intramolecular Heck cyclization as a key step. Other key features of the synthesis are *Z*-selective Wittig olefination, Sharpless asymmetric dihydroxylation followed by Williamson-type cyclo-etherification, Brown asymmetric allylation, and Noyori reduction of an alkyne. Detailed NMR study confirms the structure and stereochemistry of the synthetic maltepolide C unambiguously. However, the deviation of the spectra of the synthetic maltepolide C from those of the natural maltepolide C indicates a possible error in the original structural assignment.



In 2013, Prusov and co-workers isolated a series of unusual macrolides from the fermentation broth of the *Myxobacterium Sorangium cellulosum* So ce 1485 and named them maltepolides A–F (Figure 1).¹ The structure and absolute

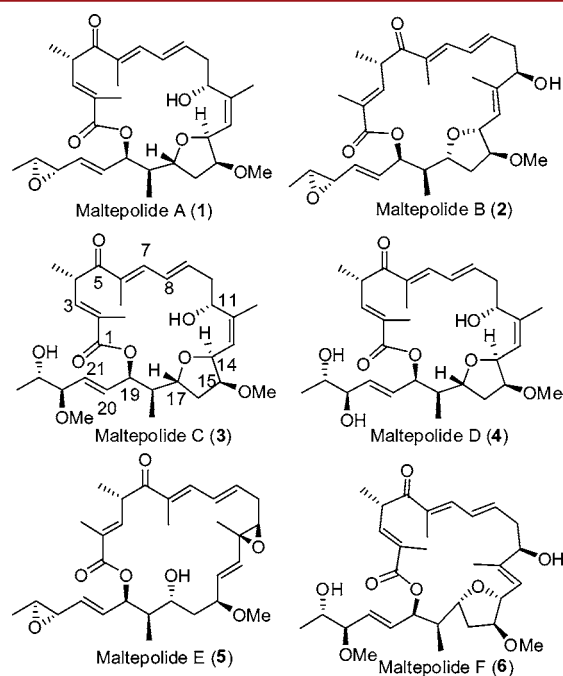


Figure 1. Structures of maltepolides A–F.

stereochemistry of maltepolides A, B, and E were confirmed via extensive NMR analysis and the Mosher ester method, whereas the absolute stereochemistry of maltepolide F (methanolysis product of maltepolide B) was unambiguously established via X-ray analysis of its di-TBS derivative. Although the structure and absolute stereochemistry of maltepolides A, B, E, and F were confirmed from detailed NMR and X-ray analysis, the

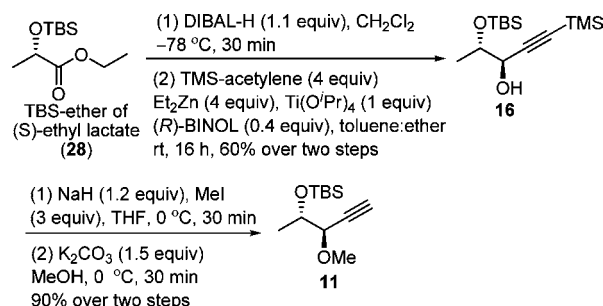
structures of maltepolides C and D were proposed via correlations of the NMR chemical shifts with those of the parent compounds. Structurally, maltepolides A–F are quite unique in nature, containing either a tetrahydrofuran ring or vinylic epoxide in the macrolactone ring. A panel of cell lines was screened against all of the maltepolides, and it was found that maltepolide C has potent cytostatic activity ($2.5 \mu\text{g mL}^{-1}$). In spite of its potent cytostatic activity and attractive architecture, surprisingly except for one synthetic study,² so far no total synthesis has been reported in the literature. Our continuous interest in the area of total synthesis of biologically important natural products³ led us to initiate a program on the total synthesis of maltepolide C, the most potent cytostatic compound of the maltepolide family, and herein, we describe the first total synthesis of the proposed structure of maltepolide C.

Structurally, maltepolide C is a 20-membered macrolide connected to a side chain through an *E*-double bond. The macrolactone core of the molecule contains seven stereocenters, one *E,E*-diene unit, one highly substituted *Z*-olefin, one substituted *E*-olefin in conjugation with the lactone carbonyl, and a highly substituted THF moiety. From this structural information, we realized that the formation of the *E,E*-diene unit from 7 via an intramolecular Heck reaction could construct the macrocycle in the molecule (Scheme 1). The acyclic precursor 7 for intramolecular Heck cyclization could be synthesized from acid 8 and alcohol 9 via an esterification reaction. The alcohol 9 might be accessed through addition of the alkyne 11 to the aldehyde 10 to give a propargylic alcohol, which on Red-Al reduction could install the C20–C21 *E*-olefin. The aldehyde 10 could be obtained from compound 12 by means of asymmetric allylation followed by functional group interconversion. Compound 12 could derive from compound 13 by partial reduction of the ester functionality followed by *Z*-

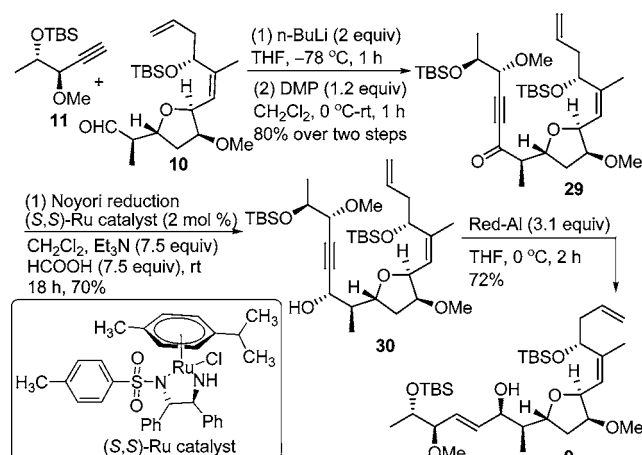
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Scheme 3. Synthesis of Alkyne 11



Scheme 4. Synthesis of Alcohol 9

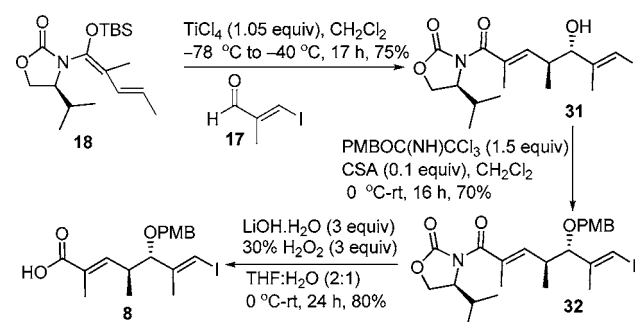


merically pure propargylic alcohol in 70% yield, which on treatment with Red-Al¹⁵ in THF at 0 °C underwent reduction of the alkyne functionality and furnished alcohol fragment 9 in 72% yield.

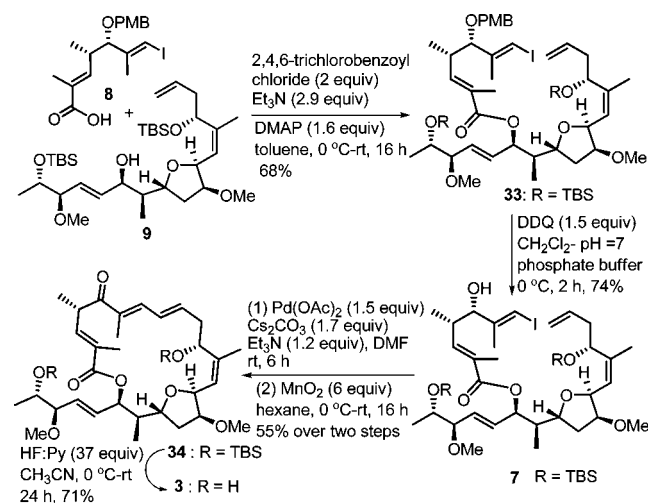
After synthesizing compound 9, we turned our attention for the synthesis of the acid fragment 8, and as per our retrosynthetic analysis, this was planned with vinylogous Mukaiyama aldol reaction developed by Kobayashi and co-workers.¹⁶ Accordingly, the known iodo acrylate 17¹⁷ was subjected to Mukaiyama aldol reaction with the enolate 18 in the presence of TiCl₄ to furnish alcohol 31^{16b} as a single isomer in 75% yield. PMB-protection of hydroxyl group in 31 with 4-methoxybenzyl-2,2,2-trichloroacetimidate, followed by removal of the chiral auxiliary with LiOOH, afforded the acid fragment 8 in 56% yield over two steps (Scheme 5).

The final strategy for completion of the synthesis of maltepolide C is depicted in Scheme 6. Esterification of the

Scheme 5. Synthesis of Acid 8



Scheme 6. Completion of the Synthesis



acid 8 with alcohol 9 under Yamaguchi conditions¹⁸ furnished compound 33 in 68% yield. PMB deprotection from compound 33 with DDQ afforded alcohol 7 in 74% yield. Now the stage was set for the crucial intramolecular Heck reaction.^{3a,17,19} Accordingly, compound 7 on treatment with Pd(OAc)₂ in the presence of Cs₂CO₃ and Et₃N in DMF furnished a highly unstable cyclized compound which, on oxidation with MnO₂, gave stable compound 34 in 55% yield over two steps. Finally, both TBS groups were deprotected with HF/Py in acetonitrile to give maltepolide C (3) in 71% yield.

A quick comparison of the ¹³C spectra (see Table 1 in the SI) of the synthetic maltepolide C with the one reported for the natural one in the literature¹ showed that they are very similar. However, a careful analysis around 57–58 ppm region (resonances arising from methoxy carbons) showed that while the reported spectra displays two ¹³C resonances overlapped at 57.9 ppm; for synthetic malepolide C (3) there are two resonances at 57.06 and 57.78 ppm. Such a difference also persisted with the ¹H spectra (see Table 2 in the SI). The reported values show that the OMe protons appear at δ 3.34 and 3.35 ppm, whereas in 3 the two methoxy resonances appear at δ 3.29 and 3.33 ppm, thus suggesting a probable conflict in the assigned configuration at the carbons attached to the methoxy groups. It was deemed necessary to find out possible structural differences in the synthesized molecule (3) and those reported for natural maltepolide C. Accordingly, detailed NMR studies in CD₃OD followed by molecular dynamics (MD) calculations were performed.

Complete assignments of the ¹H and ¹³C resonances were achieved with HSQC/HMBC experiments along with the reported data (Supporting Information). Thus, methoxy proton/carbon of –OCH₃(30) and –OCH₃(31) were assigned at 3.29/57.78 ppm and 3.33/57.06 ppm, respectively. The coupling constants ³J_{H8/H9} = 14.8 Hz and ³J_{H20/H21} = 15.6 Hz confirm the *E*-double bonds at C8–C9 and C20–C21. ³J_{H8/H9} = 14.8 Hz. Value of ³J_{H3/H4} = 11.5 Hz and the NOE correlations H3/CH₃(26) and CH₃(25)/H4 are consistent with a *E*-double bond geometry between C2 and C3 carbons. The C12–C13 *Z*-double bond was very well supported by strong NOE correlation CH₃(28)/H13. The 20-membered macrocycle appears quite rigid with most of the ³J_{H–H} <4.2 Hz or >9.5 Hz in the ring. In fact, even in the side chain C19–C24, small value of ³J_{H22/H23} = 4.2 Hz along with several

characteristic NOE correlations suggests a fair amount of rigidity. In view of this, if $^3J_{\text{H19/H20}} = 6.5$ Hz and $^3J_{\text{H21/H22}} = 8.1$ Hz and $^3J_{\text{H22/H23}} = 4.2$ Hz are assumed to arise from a single predominant conformation about the C–C bonds, corresponding to dihedral angles H19–C19–C20–H20 (θ_3) $\sim 60^\circ$, H21–C21–C22–H22 (θ_2) $\sim 180^\circ$, and H22–C22–C23–H23 (θ_1) $\sim 60^\circ$, respectively.²⁰ The observed NOE correlations H20/H22, H22/CH₃(24), H21/CH₃(24), H17/H20, and H20/CH₃(29) emphatically support the *R*-configuration at C22. Similarly, an *S*-configuration at C15 was justified by the observed couplings ($^3J_{\text{H13/H14}} = 8.2$, $^3J_{\text{H14/H15}} = 4.0$, $^3J_{\text{H15/H16a}} = 1.5$, $^3J_{\text{H15/H16b}} = 4.0$, $^3J_{\text{H16a/H17}} = 5.0$, and $^3J_{\text{H16b/H17}} = 10.5$ Hz) and NOE correlations [H16a/-OCH₃(30), H14/H16b, H13/H17, H16b/H18, H17/CH₃(29), H13/CH₃(28)] involving a tetrahydrofuran ring. One of the minimum energy structures obtained from the restrained molecular dynamics calculations, carried out using the distance constraints, derived from the NOE correlations is shown in Figure 2 (see Table 10 in the SI).

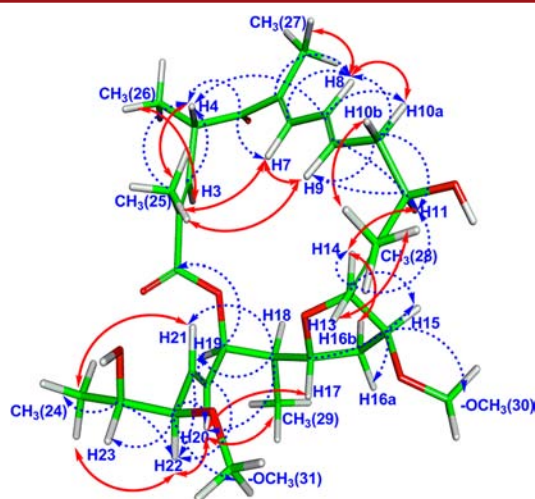


Figure 2. Characteristic HMBC correlations (dotted blue arrows) and NOE correlations (red double headed arrows) depicted in one of the minimum energy structures of **3** from the MD calculations.

Figure 2 also shows the characteristic HMBC (blue dotted arrows) and NOE (red double headed arrows) correlations. The structure thus arrived at corresponds to the one proposed by Prusov et al.,¹ which thus appears to imply that in all probability there is a need to revisit the structure of the natural product.

In conclusion, a highly convergent asymmetric total synthesis of the proposed structure of maltepolide C has been reported here for the first time. Comparison of the NMR data of **3** with those of the natural product revealed that the actual structure of maltepolide C might differ from the one proposed, thus requiring considerable synthetic efforts to solve the problem.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01981.

Experimental procedures and full spectroscopic data for compounds **3**, **7–9**, **11**, **13**, **20–26**, and **29–34** (PDF)

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Notes

The authors declare no competing financial interest.

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