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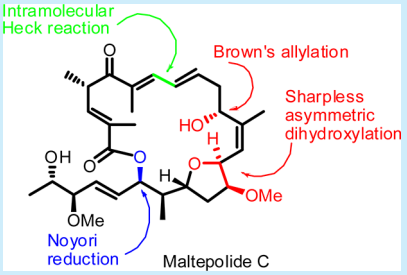
Total Synthesis of the Proposed Structure of Maltepolide C

K. Nageswara Rao,[†] M. Kanakaraju,[‡] A. C. Kunwar,[‡] and Subhash Ghosh*[,†]

[†]Organic and Biomolecular Chemistry Division and [‡]Centre for NMR & Structural Chemistry, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500007, India

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 alkynone. 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

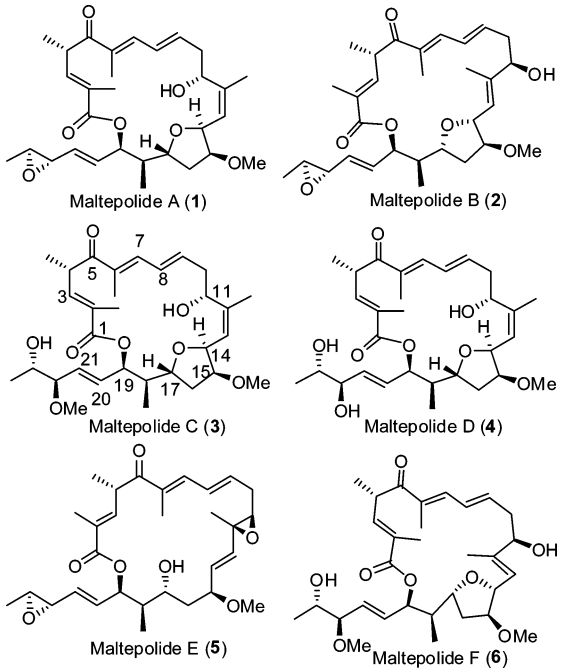


Figure 1. Structures of maltepolides A–F.

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 (methanolyis 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 μg 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 products[3] 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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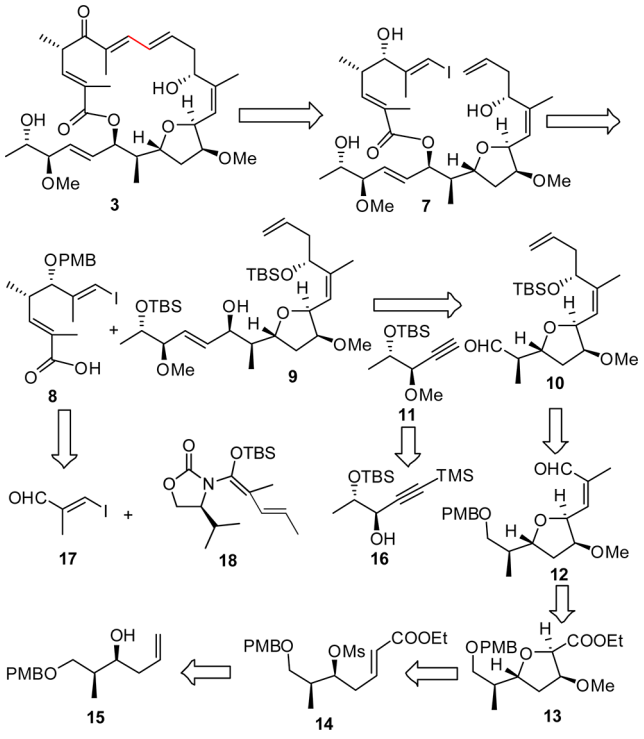
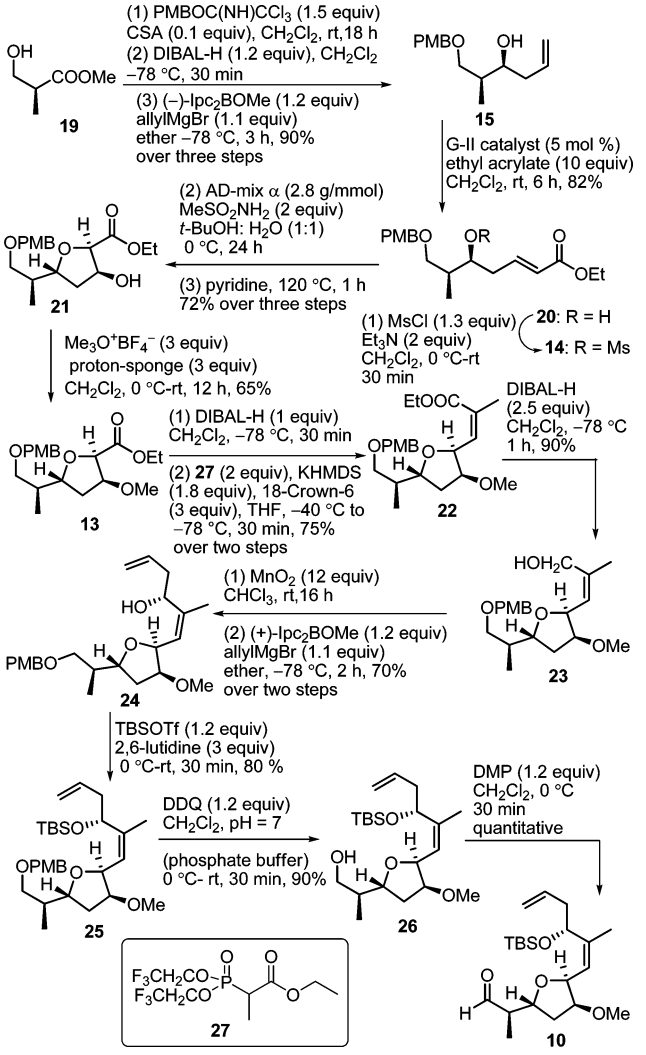
Scheme 1. Retrosynthetic Analysis of Maltepolide C



Scheme 2. Synthesis of Aldehyde 10



selective Wittig reaction and further functional group manipulation. We realized that the tetrahydrofuran ring in **13** could be accessed from compound **14** through Sharpless asymmetric dihydroxylation followed by in situ cyclo-etherification. Finally, compound **14** might be obtained from known compound **15** by means of a cross-metathesis reaction with ethyl acrylate. The acid fragment **8** could be accessed from known aldehyde **17** by way of a Mukaiyama aldol reaction.

The synthesis of aldehyde **10** (Scheme 2) commenced from known compound **15**, which was prepared from commercially available (*S*)-Roche ester **19** according to the reported procedure.[4] Cross-metathesis reaction[5] between **15** and ethyl acrylate in the presence of Grubbs second-generation catalyst in CH_2Cl_2 at room temperature produced required compound **20** in 82% yield with complete *E*-selectivity. To construct the tetrahydrofuran ring, the hydroxyl group was converted to its mesylate with MsCl and Et_3N, and then the corresponding mesyl compound **14** was subjected to dihydroxylation. From our previous experience[3a] and also from a literature report,[2] we realized that under dihydroxylation conditions hydroxylation followed by in situ cycloetherification could lead to the formation of the tetrahydrofuran ring. However, to our surprise, under dihydroxylation conditions cycloetherification reaction did not take place. Gratifyingly, the crude diol compound on stirring at 120 °C in pyridine underwent cycloetherification reaction smoothly and provided the desired product **21** (dr = 18:1) in 72% yield over three steps.[6] Methylation of the hydroxyl group in **21** with Ag_2O[7a] and methyl iodide afforded the required product in poor yield (<30%). However, with trimethyloxonium tetrafluoroborate and Proton Sponge,[7b] the methylation reaction proceeded smoothly and provided compound **13** in 65% yield. To construct the C12−C13 *Z*-olefinic moiety, the ester group of compound **13** was subjected to partial reduction with DIBAL-H to furnish an aldehyde, which on reaction with Still−Gennari phosphonate (**27**)[8] in the presence of KHMDS in THF provided chromatographically pure compound **22** in 75% yield over two steps. The ester functionality in **22** was reduced with DIBAL-H to give alcohol **23** (90%) which, on oxidation with MnO_2,[9] followed by Brown asymmetric allylation of the resulting aldehyde, afforded secondary alcohol **24** (dr > 20:1) in 70% over two steps. Alcohol **24** on protection with TBS-OTf furnished compound **25** (80%), which on PMB deprotection under buffered DDQ conditions yielded the primary alcohol **26** in 90% yield.[10] Finally, oxidation of the primary alcohol with DMP in CH_2Cl_2 furnished the aldehyde **10** in quantitative yield.[11]

The alkyne fragment **11** was synthesized from the known compound **16**[12] in two steps as shown in Scheme 3. Methylation of alcohol **16** with MeI[13] followed by TMS deprotection under K_2CO_3/MeOH conditions completed the synthesis of the alkyne fragment **11**.

After synthesizing the aldehyde **10** and alkyne **11**, our next objective was to couple them to obtain the alcohol **9** (Scheme 4). Accordingly, anion generated from **11** with *n*-BuLi was added to the aldehyde **10** to give an inseparable diastereomeric mixture (2.5:1) of propargylic alcohols which on oxidation with DMP afforded alkynone **29** in 80% over two steps.

Asymmetric reduction of the keto functionality in **29** was carried out under Noyori conditions[14] to provide diastereo-

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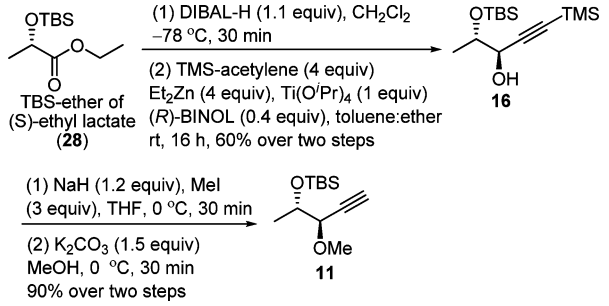
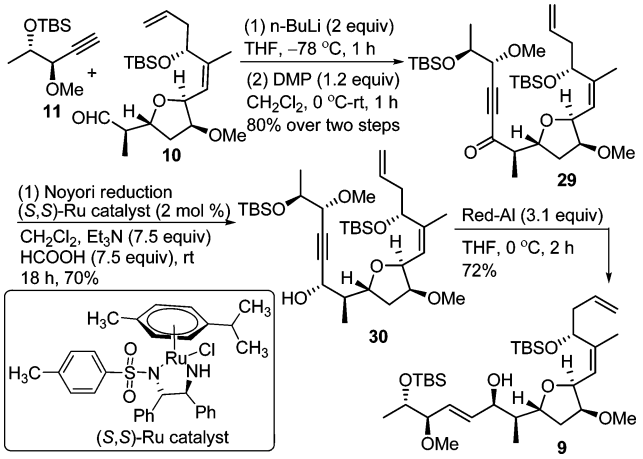
Scheme 3. Synthesis of Alkyne 11



Scheme 4. Synthesis of Alcohol 9

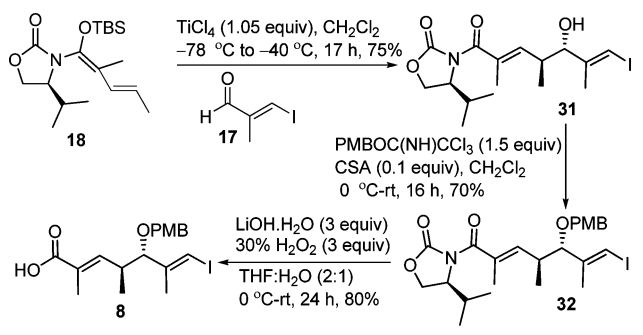


merically pure propargylic alcohol in 70% yield, which on treatment with Red-Al[15] in THF at 0 °C underwent reduction of the alkyne functionality and furnished alcohol fragment **9** in 72% yield.

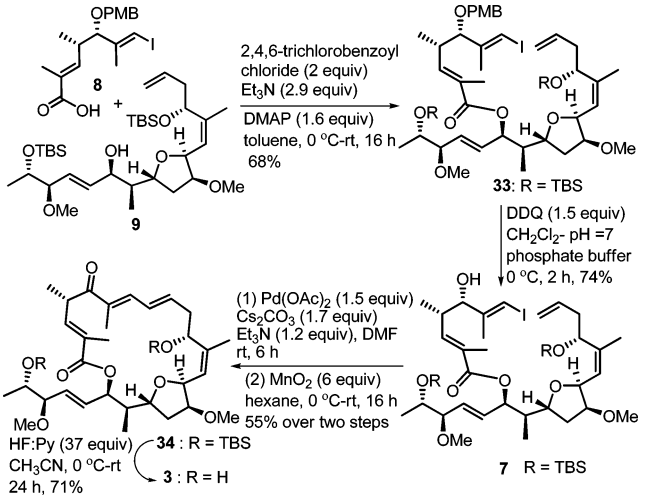
After synthesizing compound **9**, we turned our attention for the synthesis of the acid fragment **8**, and as per our retrosythetic analysis, this was planned with vinylogous Mukaiyama aldol reaction developed by Kobayashi and co-workers.[16] Accordingly, the known iodo acrylate **17**[17] was subjected to Mukaiyama aldol reaction with the enolate **18** in the presence of $TiCl_4$ 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 conditions[18] 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 Cs_2CO_3 and Et_3N in DMF furnished a highly unstable cyclized compound which, on oxidation with MnO_2, 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 ^{13}C spectra (see Table 1 in the SI) of the synthetic maltepolide C with the one reported for the natural one in the literature[1] 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 ^{13}C 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 ^{1}H 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 felt necessary to find out possible structural differences in the synthesized molecule (**3**) and those reported for natural maltepolide C. Accordingly, detailed NMR studies in CD_3OD followed by molecular dynamics (MD) calculations were performed.

Complete assignments of the ^{1}H and ^{13}C resonances were achieved with HSQC/HMBC experiments along with the reported data (Supporting Information). Thus, methoxy proton/carbon of $-OCH_3(30)$ and $-OCH_3(31)$ were assigned at 3.29/57.78 ppm and 3.33/57.06 ppm, respectively. The coupling constants $^{3}J_{H8/H9}$ = 14.8 Hz and $^{3}J_{H20/H21}$ = 15.6 Hz confirm the *E*-double bonds at C8−C9 and C20−C21. $^{3}J_{H8/H9}$ = 14.8 Hz. Value of $^{3}J_{H3/H4}$ = 11.5 Hz and the NOE correlations H3/CH_3(26) and CH_3(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 CH_3(28)/H13. The 20-membered macrocycle appears quite rigid with most of the $^{3}J_{H-H}$ <4.2 Hz or >9.5 Hz in the ring. In fact, even in the side chain C19−C24, small value of $^{3}J_{H22/H23}$ = 4.2 Hz along with several

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characteristic NOE correlations suggests a fair amount of rigidity. In view of this, if $^3J_{H19/H20}$ = 6.5 Hz and $^3J_{H21/H22}$ = 8.1 Hz and $^3J_{H22/H23}$ = 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) ∼ 60°, H21−C21−C22−H22 (θ_2) ∼ 180°, and H22−C22−C23−H23 (θ_1) ∼ 60°, respectively.[20] The observed NOE correlations H20/H22, H22/CH_3(24), H21/CH_3(24), H17/H20, and H20/CH_3(29) emphatically support the *R*-configuration at C22. Similarly, an *S*-configuration at C15 was justified by the observed couplings ($^3J_{H13/H14}$ = 8.2, $^3J_{H14/H15}$ = 4.0, $^3J_{H15/H16a}$ = 1.5, $^3J_{H15/H16b}$ = 4.0, $^3J_{H16a/H17}$ = 5.0, and $^3J_{H16b/H17}$ = 10.5 Hz) and NOE correlations [H16a/-OCH_3(30), H14/H16b, H13/H17, H16b/H18, H17/CH_3(29), H13/CH_3(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).

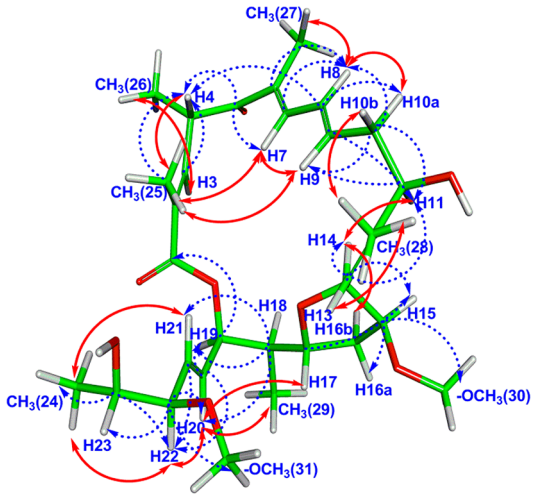

Figure 2. Characteristic HMBC correlations (dotted blue arrows) and NOE correlations (red double headed arrows) depicted in one of the minimum energy structures of **3** from the MD calculations.

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)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: subhash@iict.res.in.

Notes

The authors declare no competing financial interest.

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