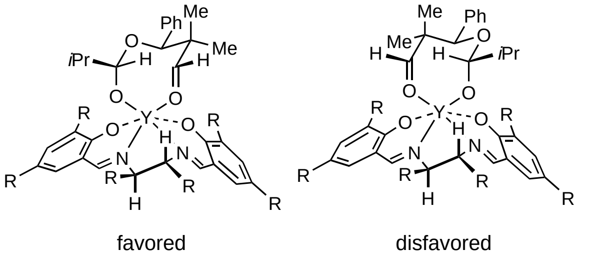

Scheme 2. Predictive model for enantioselection in the aldol-Tishchenko reaction catalyzed by Y–salen complexes.

from the axial salen hydrogen; presumably the diastereomeric transition structure suffers from this steric interaction thereby yielding less of the minor enantiomer.

In conclusion, we have discovered and developed the first catalytic enantioselective aldol-Tishchenko reaction. The mechanistic studies presented herein should provide a useful starting point for the development of more effective catalytic asymmetric aldol-Tishchenko reactions.

Received: October 9, 2000 [Z15926]

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[14] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-150468. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[15] Crystals were obtained by allowing acetone to diffuse into a 1:1 (metal:ligand) mixture of $Y_5O(OiPr)_{13}$ and ligand **1a** in dichloromethane. The bridging hydroxides likely result from adventitious moisture. According to the X-ray analysis, one acetone is pyramidalized such that it might be construed as an isopropoxide. We feel that this is unlikely since it requires one bridging ligand to be a water molecule in order to maintain the Y^{III} oxidation state.

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Total Synthesis of the Callipeltoside Aglycon[**]

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Rodolfo Marquez

The callipeltosides were isolated by Minale and co-workers from the shallow-water lithistid sponge *Callipelta* sp., collected off the east coast of New Caledonia.[1a,b] Callipeltoside A (**1** in Scheme 1, obtained in 1.4×10^{-4}% yield) was found to inhibit in vitro the proliferation of KB and P388 cells (IC_{50} values of 11.26 and 15.26 $\mu g\,mL^{-1}$, respectively). Results indicate this activity to be cell-cycle dependent, blocking proliferation in the G1 phase, highlighting callipeltoside A as a putative, mechanism-based lead.[1a] Similarly, callipeltosides B and C, differing only in the sugar portion of their structures, also exhibited marked cytotoxic activity.[1b]

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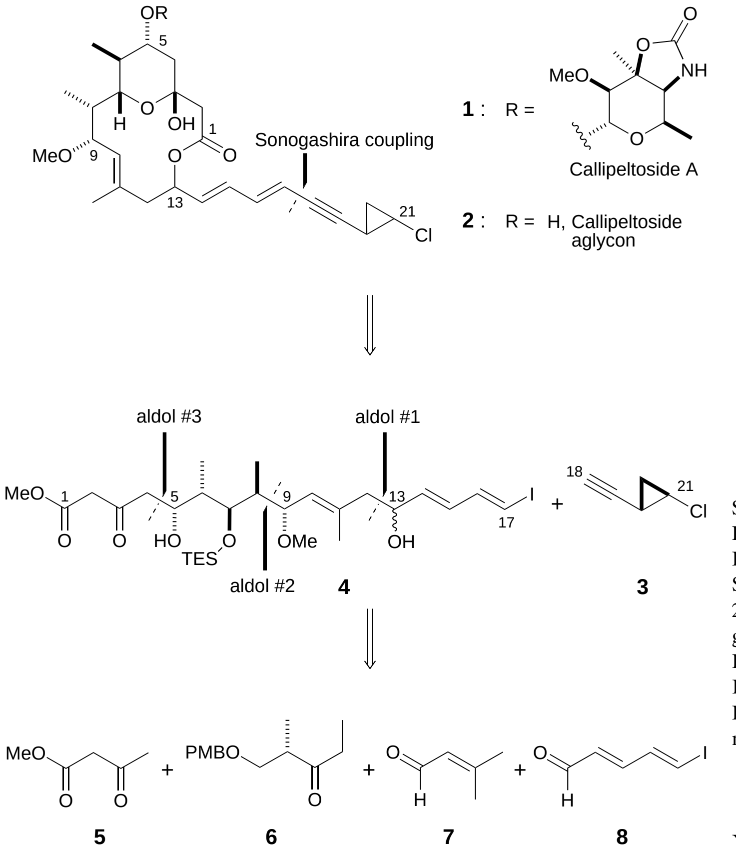
[**] We thank the EPSRC (R.D.M.D; GR/N08520), Girton College, Cambridge (R.M.), and Merck for support, and Setu P. Roday (Cambridge) for kindly assisting with the molecular modeling studies.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

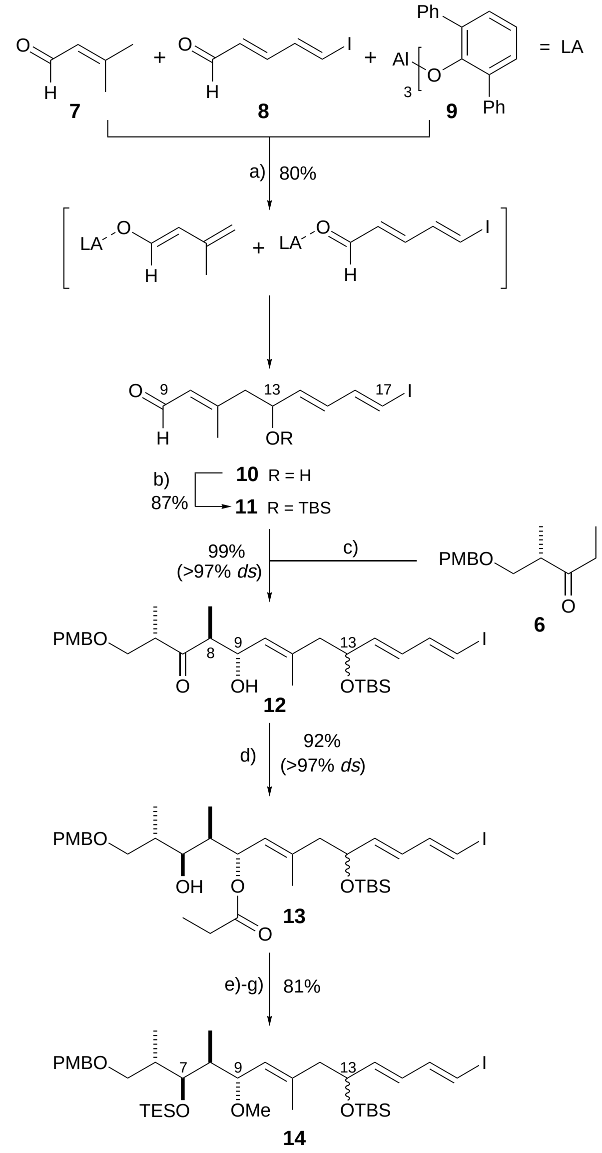
1433-7851/01/4003-0603 $ 17.50+.50/0

From extensive two-dimensional NMR analysis, the callipeltoside aglycon (**2**, Scheme 1)[1c] was characterized structurally as a unique hemiacetal-containing, 14-membered, macrolide with seven stereocenters and an *E*-trisubstituted alkene. The pendant unsaturated side chain is an unusual feature of this rare marine polyketide, comprising a *trans*-chlorocyclopropane ring adjacent to a dienyne system. Whilst the relative configuration of the callipeltosides has been partly assigned,[1c] synthetic efforts[2] are required to resolve the remaining structural ambiguities, and ultimately provide access to additional material for biological evaluation. Herein, we report the first total synthesis of the callipeltoside aglycon (**2**). By adopting a pragmatic approach to stereocontrol and utilizing contemporary aldol methodology, we have synthesized two epimers that differ only in the configuration at C13 and elucidated the relative configuration within the macrolide ring.

Our synthetic plan relied on the late-stage Sonogashira coupling of alkyne **3** (or *ent*-**3**), preceded by hemiacetalization and macrolactonization, which leads back to the acyclic C1–C17 fragment **4**. This can be further dissembled by three strategic aldol disconnections at C4–C5, C8–C9 and C12–C13, giving *β*-keto ester **5**, chiral ketone **6** and aldehydes **7** and **8**.



Scheme 1. Retrosynthetic analysis of the callipeltoside aglycon (**2**). PMB = *para*-methoxybenzyl.

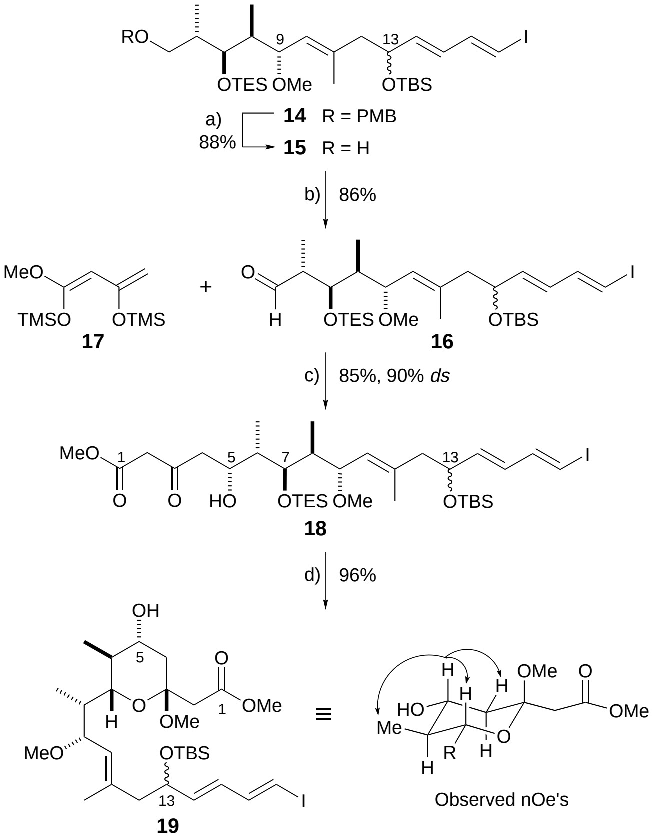


Scheme 2. Synthesis of the C5–C17 subunit **14**: a) toluene, −78 °C, 5 min; LDA, THF, −78 °C, 15 min; b) TBSCl, Im, CH_2Cl_2, 20 °C, 1 h; c) 1) (*c*-Hex)$_2$BCl, Et_3N, Et_2O, −5 °C, 1 h; **11**, −78 → −27 °C, 16 h; 2) CH_2Cl_2/H_2O, SiO_2, 20 °C, 30 min; d) SmI_2, EtCHO, THF, −20 → −10 °C, 2 h; e) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h; f) DIBAL, CH_2Cl_2, −78 °C, 30 min; g) Me_3OBF_4, H^+ sponge, CH_2Cl_2, 0 → 20 °C, 1 h. *c*-Hex = cyclohexyl, LDA = lithium diisopropylamide, TBSCl = *tert*-butyldimethylsilyl chloride, Im = imidazole, TESOTf = triethylsilyl trifluoromethanesulfonate, DIBAL = diisobutylaluminum hydride, H^+ sponge = 1,8-bis(dimethylamino)napthalene-*N*,*N*,*N'*,*N'*-tetramethyl-1,8-napthalenediamine.

A key objective in the synthesis was to install the *E*-trisubstituted alkene at an early stage. We achieved this (Scheme 2) using the vinylogous aldol reaction developed by Yamamoto et al., which is promoted by the aluminum Lewis acid **9**.[3] Hence, the extended enolate of enal **7** was added to the readily available *E*,*E*-configured iododiene aldehyde **8**[4] to provide the C9–C17 subunit **10** in 80 % yield, with complete control of double bond geometry. Notably, this opening gambit permitted the flexibility required at the C13 center, whilst incorporating the iododiene precursor to the callipeltoside side chain, latterly to be appended with the cyclopropyl alkyne **3**. However, the survival of this delicate functionality was to be a key concern throughout the remainder of the synthesis.

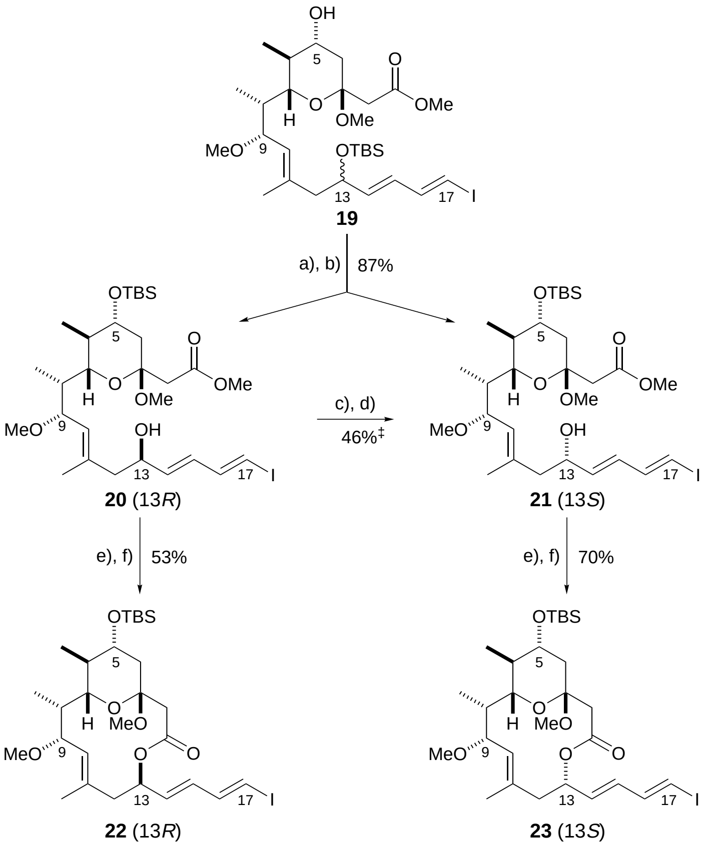
Protection of aldol adduct **10** as the corresponding TBS ether furnished aldehyde **11**. Application of our boron-mediated anti-aldol reaction[5] to ethyl ketone **6**[6] and aldehyde **11** gave adducts **12** in 99 % yield and complete selectivity at C8 and C9. The usual oxidative cleavage of the initially formed boronate product with H_2O_2 was found to be incompatible with the iododiene functionality, necessitating an alternative hydrolytic cleavage over silica gel.[7] At this stage, the mixture of C13 epimers was not readily separable. An Evans–Tishchenko reduction[8] with SmI_2 and propionaldehyde formed exclusively the 1,3-*anti* diol, protected as the monopropionate **13**. Subsequent TES protection of the C7 hydroxyl, reductive removal of the propionate ester with DIBAL and methylation at the C9 hydroxyl afforded triene **14** (see Scheme 2).

Oxidative removal of the PMB protecting group in **14** (Scheme 3) with DDQ, in the presence of the allylic TBS ether at C13, proved to be problematic. Unwanted oxidation of the latter functionality to the dienone,[9] as well as substrate instability to the reaction conditions were observed. These issues were ameliorated by refluxing **14** in CH_2Cl_2/pH 7 buffer with DDQ (1 equiv) to provide alcohol **15** (42 %; 88 % based on recovered starting material). With alcohol **15** in hand, Dess–Martin oxidation provided aldehyde **16**, primed for the final aldol reaction needed to introduce the C5 stereocenter. Indeed, a Mukaiyama aldol reaction, promoted by $BF_3 \cdot OEt_2$, between the O-silylated dienolate **17**[10] and the α-chiral aldehyde **16** proceeded with Felkin–Anh control[11] to give β-keto ester **18** in 85 % yield and 90 % diastereoselectivity. Treatment of **18** with PPTS and trimethyl orthoformate in MeOH effected selective TES deprotection with concomitant methyl acetal formation to provide **19**, allowing assignment of the configuration by NOE analysis.



Scheme 3. Synthesis of the C1–C17 subunit **19**: a) DDQ (1 equiv), CH_2Cl_2/pH 7 buffer (10/1), 40 °C, 10 min; b) DMP, CH_2Cl_2, 20 °C, 1 h; c) $BF_3 \cdot OEt_2$, CH_2Cl_2, −100 °C, 15 min; d) PPTS, $(MeO)_3CH$, MeOH, 20 °C, 2 h. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMP = Dess–Martin periodinane.

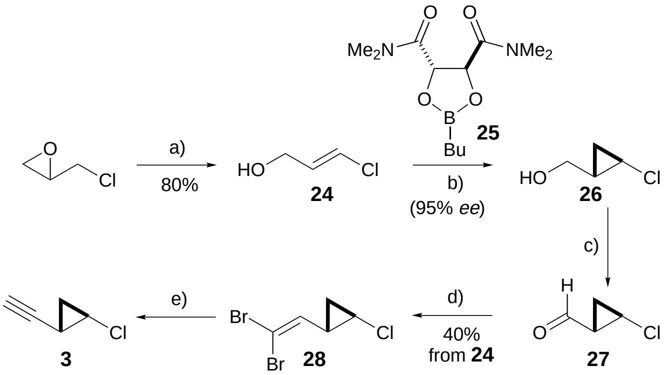
The subsequent TBS protection of the C5 hydroxyl in **19** (Scheme 4) proved significant, as the selective deprotection of the allylic TBS ether at C13 by TBAF revealed alcohols **20** (13*R*) and **21** (13*S*), which were now separable by regular flash column chromatography. At this point, the absolute configuration at C13 was assigned by ^1H NMR MTPA analysis using the advanced Mosher method.[12]



Scheme 4. Synthesis of the C1–C17 macrolides **22** and **23**: a) TBSCl, Im, CH_2Cl_2, 20 °C, 2 h; b) TBAF, THF, 20 °C, 1 h; c) TPAP, NMO, 4 Å molecular sieve, CH_2Cl_2, 20 °C, 50 min; d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, −78 → 0 °C, 40 min; e) $Ba(OH)_2 \cdot 8H_2O$, MeOH, 20 °C, 16 h; f) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 80 °C, 4 h. TBAF = tetrabutylammonium fluoride, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine, DMAP = 4-(*N*,*N*-dimethylamino)pyridine. The reduction gave an approximately 1:1 mixture of **21** and **20**.

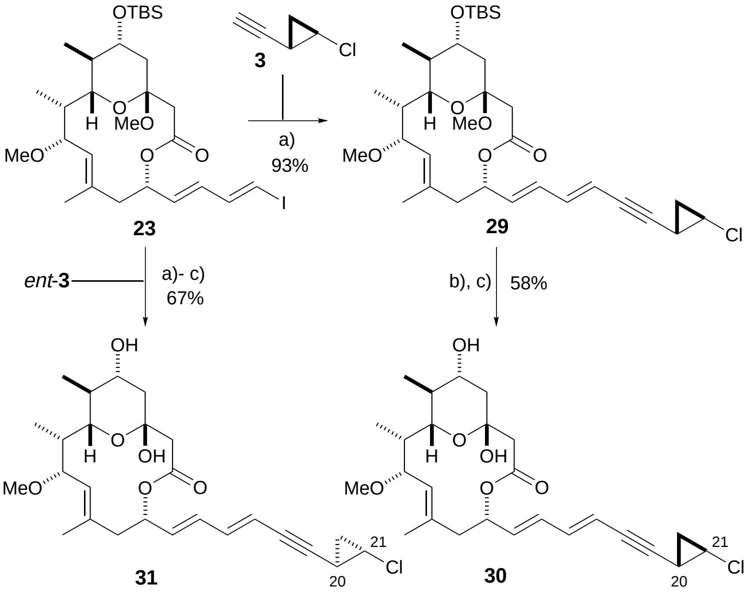
In parallel studies, saponification of the methyl esters **20** and **21** with barium hydroxide, followed by the key macrolactonization, provided, after optimization, the diastereomeric macrolides **22** (53 %) and **23** (70 %), respectively. We first employed the Yonemitsu[13] variant of the Yamaguchi lactonization[14] on **20**, which resulted in the formation of mostly macrodiolides and -triolides, with monomer **22** as a minor component. We then turned to the conventional Yamaguchi protocol which, with the careful control of temperature (80 °C) and slow addition, proved successful.[15] Before embarking on the synthesis, we probed the configuration at C13 of the two possible diastereomeric macrolides by molecular modeling.[16] By comparing the reported NOE data[1a] with the calculated global minimum energy conformation, we found **23** to be the more likely candidate. Subsequent comparison of macrocycles **22** and **23** by ^{1}H NMR spectroscopy reinforced this conclusion: The spectrum and NOE data of the latter closely matched that recorded for the callipeltosides. At this point, the unwanted diastereomer **20** could be converted to give more of **21** by oxidation with TPAP,[17] followed by Luche reduction.[18]

Having assembled the desired 14-membered macrolide **23**, we addressed introduction of the full side chain. The synthesis of alkyne **3** (Scheme 5) commenced with the treatment of *epi*-chlorohydrin with *n*BuLi in the presence of TMEDA, which generated chloroallylic alcohol **24** in 80 % yield as a single geometric isomer.[19] Asymmetric Simmons–Smith cyclopropanation under the conditions of Charette et al.,[20] using the dioxaborolane ligand **25** derived from (*S*,*S*)-(−)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide, supplied alcohol **26** in 95 % *ee* (^{19}F NMR MTPA analysis). In an analogous fashion, the enantiomeric alcohol, *ent*-**26**, was prepared with the (*R*,*R*)-(+)-dioxaborolane ligand. Swern oxidation of **26** gave aldehyde **27**, which was treated under Corey–Fuchs conditions[21] to generate dibromo olefin **28** (40 % from **24**). Lastly, treatment of **28** with *n*BuLi provided alkyne **3**. The antipodal cyclopropane, *ent*-**3**, was prepared in an identical fashion.



Scheme 5. Synthesis of the C18–C22 alkyne **3**: a) *n*BuLi, TMEDA, THF, −78 → 0 °C, 1.5 h; b) ZnEt$_2$, CH$_2$I$_2$, chiral auxiliary **25**, CH$_2$Cl$_2$, 0 → 20 °C, 16 h; c) (COCl)$_2$, DMSO, CH$_2$Cl$_2$, −78 °C, 20 min; Et$_3$N, −78 → 0 °C, 20 min; d) Zn, py, PPh$_3$, CBr$_4$, CH$_2$Cl$_2$, 20 °C, 16 h; e) *n*BuLi, Et$_2$O, −78 °C, 30 min. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, DMSO = dimethylsulfoxide, py = pyridine.

After removing the ether solvent at atmospheric pressure, **3** was used directly in the Sonogashira coupling with the macrocyclic dienyl iodide **23** (Scheme 6). Conventional coupling conditions ([Pd(PPh$_3$)$_4$], CuI, *n*BuNH$_2$ in benzene)[22] failed to generate any of the desired product **29**. However, conditions developed for the coupling of electron defficient alkynyl amides[23] [(Ph$_3$P)$_2$PdCl$_2$], CuI, *i*Pr$_2$NH, in ethyl acetate) proved successful, affording the protected aglycon **29** in 93 % yield with retention of double bond geometry. Finally, deprotection of the TBS ether with TBAF, followed by treatment with catalytic PPTS in wet acetonitrile to hydrolyse the methyl acetal, provided the callipeltoside aglycon **30**. Similarly, the enantiomeric cyclopropyl alkyne *ent*-**3** was coupled with **23** and deprotected to provide the diastereomeric aglycon **31**.



Scheme 6. Synthesis of the callipeltoside aglycons **30** and **31**: a) [(PPh$_3$)$_2$PdCl$_2$], CuI, *i*Pr$_2$NH, EtOAc, −20 → 20 °C, 1.5 h; b) TBAF, THF, 20 °C, 50 min; c) PPTS, CH$_3$CN, H$_2$O, 20 °C, 16 h.

Although the ^{1}H and ^{13}C NMR spectra of these diastereomers were essentially identical, there was a substantial difference in optical rotation: **30** had $[\alpha]^{D}_{20} = -97.8$ ($c = 0.19$, CHCl$_3$) and **31** had $[\alpha]^{D}_{20} = +45.8$ ($c = 0.28$, CHCl$_3$).[24] The 500 MHz ^{1}H NMR spectra of both **30** and **31** matched closely with those recorded[1b] for the callipeltosides in CDCl$_3$, with divergence in the signals of and around C5 due to the absence of a sugar moiety. The ^{13}C NMR spectrum also showed close agreement with the reported data, except for the C20 and C21 resonances of the cyclopropane ring.[25]

In conclusion, this expedient total synthesis of the callipeltoside aglycon proceeds in 20 steps and 2.7 % yield from pyridinium-1-sulfonate (precursor to **8**)[4] for the longest linear sequence. Attachment of the sugar residue to aglycons **30** and **31** should enable the full stereochemical assignment of callipeltoside A. This work represents the first application of Yamamoto's vinylogous aldol in total synthesis, which has proved highly effective applied in tandem with our own selective boron-mediated aldol methodology. The early incorporation of the delicate iododiene functionality for a late-stage Sonogashira coupling is also noteworthy.

Received: November 9, 2000 [Z16070]

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[25] See the Supporting Information for ^{1}H and ^{13}C NMR data of **30** and **31**. The chemical shift reported for the chlorine bearing carbon C21, within the cyclopropane ring of the callipeltosides, was $\delta = 55.4$ with the C9 methoxy group adjacent at 55.2. However, in our aglycons **30** and **31**, only one resonance is present at $\delta \approx 55$, which is assigned to the methoxy group; furthermore, HMQC (heteronuclear multiple-quantum coherence) analysis of **30** showed the C21 resonance to be at $\delta = 34.2$. In the callipeltosides a resonance at $\delta = 34.0$ was attributed to the remaining C20 methine. In actual fact, the signal of the C20 methine in the aglycons **30** and **31** lies at $\delta = 12.02$, almost coinciding with the C25 methyl signal at $\delta = 11.98$, which were resolved by a DEPT 90 NMR experiment. Thus, we conclude that the ^{13}C NMR spectra of the callipeltosides may require the reassignment of C20 ($\delta = 12.0$) and C21 ($\delta = 34.0$). For supportive ^{13}C NMR spectral data on chlorocyclopropanes, see: Y. Kusuyama, T. Kagosaku, T. Hasegawa, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2836.

Insights into the Branched-Chain Formation of Mycarose: Methylation Catalyzed by an (*S*)-Adenosylmethionine-Dependent Methyltransferase[**]

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Methylation is a common biotransformation that encompasses a wide variety of substrates involved in a myriad of biological processes.[1] For example, methylation of DNA has been shown to play an important role in gene regulation, and methylation of specific protein targets has been established as a general mechanism to control signal transduction or cell growth and differentiation. In addition, the biological consequences of methylation of rRNA and mRNA are also well documented.[1] The majority of biological methyl transfers are catalyzed by methyltransferases that use (*S*)-adenosylmethionine (AdoMet) as the methyl donor. It is of interest that methylation is such a prevalent process in living organisms, considering that methyl transfer from AdoMet to its acceptor is intrinsically a very slow reaction in water.[2] Although methyltransferases characteristically display low k_{cat} values, their catalysis of methyl transfer can still be considered significant compared to the uncatalyzed reaction.

While the flexibility of AdoMet as a methyl donor is apparent from its ability to use carbon, nitrogen, and oxygen as acceptors, methyltransferases that are capable of catalyzing C-methylation are much less common and therefore less well studied.[3] A specific area in which C-methyltransferases

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[**] We are grateful to Dr. Eugene Seno and the Lilly Research Laboratories for their generous gift of the plasmid pHJL311 and to the National Institutes of Health for grants (GM 35906 and 54346). H.-w.L. also thanks the National Institute of General Medical Sciences for a MERIT Award. T.M.H. was a trainee of the National Institute of General Medical Sciences (Biotechnology Training Grant: 2 T32 GM08347).