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Studies directed toward the synthesis of the massileunicellins

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Abstract—An approach to the massileunicellins is described that employs a cycloaldol reaction to assemble the isobenzofuran bicyclic core. A stereoselective rearrangement–epoxidation–oxidation cascade and a chelation controlled addition to a hindered acyl furan are used to install the C3, C11, C12, and C13 oxygens. The synthesis establishes eight of the nine stereocenters present in the isobenzofuran core of the massileunicellins.

The massileunicellins are a family of densely functionalized eunicellin diterpenes that possess an isobenzofuran core in which all eight of the ring carbons are stereocenters (Fig. 1).[1,2] In addition, they possess a tertiary alcohol stereocenter at C3 adjacent to the furan ring. A key challenge facing any projected synthesis will be the efficient and stereocontrolled introduction of the four oxygen containing stereocenters at C3, C11, C12, and C13.

We recently reported a cycloaldol approach to the isobenzofuran cores of less highly functionalized eunicellins.[3] We describe herein the first reported efforts toward the synthesis of the most stereochemically complex members of the eunicellin diterpenes.[4–6]

We anticipated that the oxonane ring of our first target, massileunicellin D, could be formed late in the synthesis via aldehyde **2** (Scheme 1). We reasoned that an alkyne functionality at C4–C5 would offer a synthetically flexible handle for closure of the oxonane ring by a variety of possible strategies. The aldehyde should be accessible from epoxide **3** via base-mediated ring opening of the epoxide followed by reduction of the resulting C9–C10 alkene. Epoxide **3** in turn could be prepared from keto alkene **4**, with the C3–C4 alkene serving as a precursor to a methyl ketone. The keto alkene could be derived from 3° allylic alcohol **5**, which could be synthesized

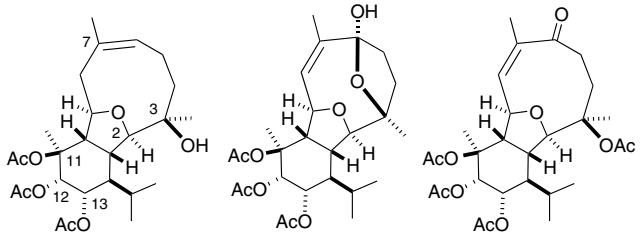
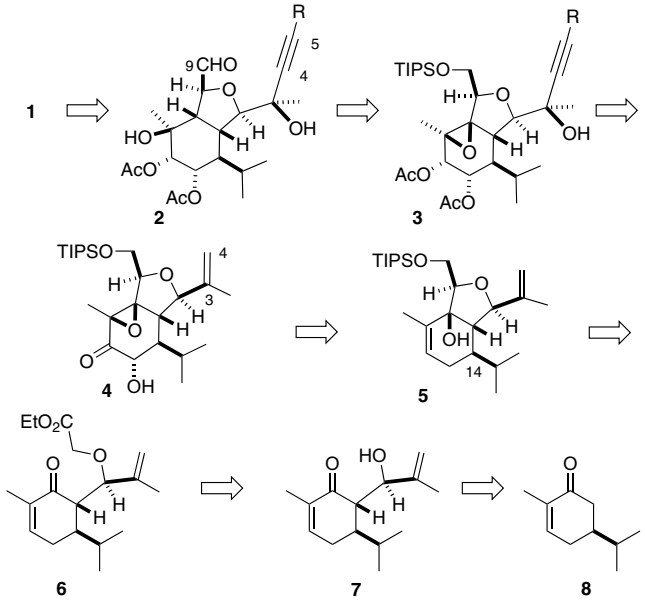


Figure 1. Massileunicellins C, D, and K (**1**).



Scheme 1.

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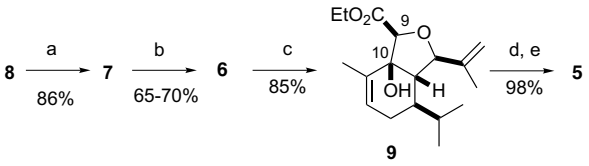


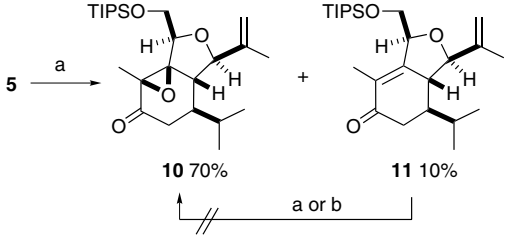
Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, methacrolein, HOAc; (b) Ag_2O, $BrCH_2CO_2$ Et, 2,6-lutidine, DMF, 4 °C, 7 d; (c) KHMDS, THF, −78 °C; (d) LAH, ether, −78 °C; (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2.

from (*S*)-dihydrocarvone[7] (**8**) via an aldol–cycloaldol sequence.

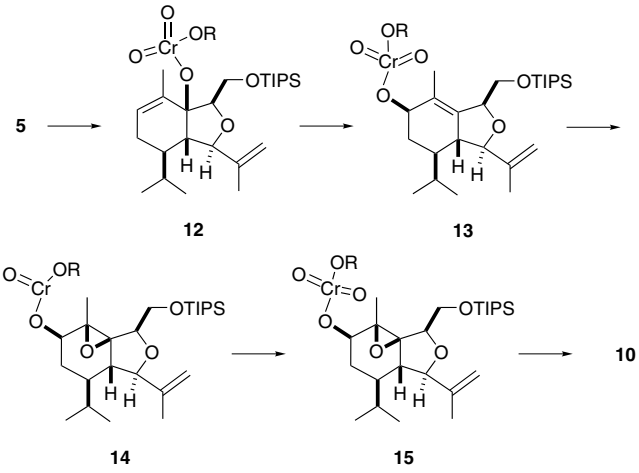
We have previously reported the synthesis of an isobenzofuran directly analogous to **5** that possesses a C14 isopropenyl susbstituent.[3] Alcohol **5**, possessing the C14 isopropyl substituent, was prepared from (*S*)-carvone in four steps (Scheme 2). Aldol reaction of (*S*)-dihydrocarvone[7] (**8**) with methacrolein followed by etherification gave glycolate **6**. Cycloaldolization of keto glycolate **6** then yielded isobenzofuran **9** in 85% yield.[8] Reduction of the ester and protection then afforded TIPS ether **5**.

Our original synthetic strategy entailed an oxidative rearrangement of allylic alcohol **5** to enone **11** (Scheme 3). In the course of optimizing the oxidative rearrangement, we found that treatment of allylic alcohol **5** with PCC and NaOAc led directly to epoxy ketone **10** in preparatively useful yield. This one-step conversion of allylic alcohol **5** to epoxy ketone **10** is the first example of a stereo- and regioselective variant of this transformation (vide infra).

Resubjection of enone **11** to the reaction conditions returned only starting material. The lack of conversion of enone **11** into epoxide **10** using PCC/NaOAc suggests that an allyloxy Cr(VI) intermediate is the epoxide precursor (Scheme 4). The mechanism presumably



Scheme 3. Reagents and conditions: (a) PCC, NaOAc, CH_2Cl_2, rt; (b) H_2O_2, NaOH, H_2O, MeOH.



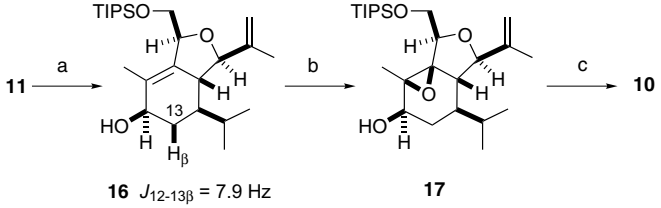
Scheme 4.

involves formation of a 3° Cr(VI) ester such as **12** followed by [3,3]-rearrangement (or ionization–readdition) to 2° Cr(VI) ester **13**. Epoxidation of the allylic alkene by the Cr(VI) ester would afford the Cr(IV) ester epoxide **14**. Exchange of Cr(IV) ester **14** to Cr(VI) ester **15** is presumably required for oxidation to ketone **10**.

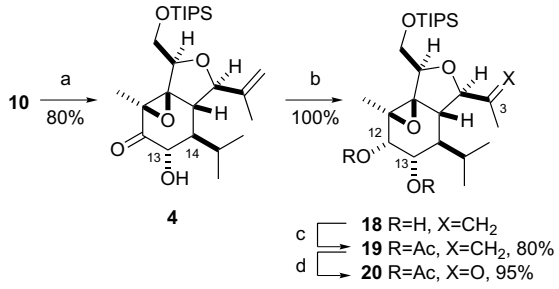
This result has precedent in the work of Sundararaman and Herz,[9] who found that oxidation of acyclic 3° allylic alcohols with Collins reagent [$CrO_3(pyr)_2$] gave moderate to good yields of rearranged epoxy aldehydes albeit with no relative stereocontrol at the epoxide stereocenters. Ishihara et al. later reported that rearranged epoxy alcohols were the major products upon treatment of [5.3.0]carbobicyclic allylic alcohols with PCC.[10,11] However, the reaction lacked both regio- and stereocontrol with respect to preexisting stereocenters.

The oxidative rearrangement–epoxidation sequence has several noteworthy features. Attempts at nucleophilic epoxidation of enone **11** under standard conditions (H_2O_2, NaOH) returned only starting material, presumably due to the sterically hindered nature of the enone.[12,13] Thus the reaction may allow for the formation of epoxy ketones that are not otherwise readily accessible. Furthermore, it avoids the use of strong base that may cause undesired side reactions such as enolization or hydrolysis. Finally, it is inherently more efficient than the two step procedure.

The stereochemistry of the epoxide was confirmed by independent synthesis using directed epoxidation (Scheme 5). Axially selective reduction of enone **11** gave



Scheme 5. Reagents and conditions: (a) LAH, ether, −78 °C, 100%; (b) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 60%; (c) PCC, CH_2Cl_2, 89%.



Scheme 6. Reagents and conditions: (a) KHMDS, TMSCl, ether, −78 °C; *m*CPBA, hexanes, $NaHCO_3$, −20 °C; (b) LiHAl(O-*t*-Bu)$_3$, ether, −78 °C to rt; (c) Ac_2O, NEt_3, DMAP, CH_2Cl_2; (d) O_3, PPh_3, CH_2Cl_2/MeOH, −78 °C.

C12 β-alcohol **16**. The stereochemistry of reduction was assigned on the basis of the $J_{12-13\beta}$ coupling (7.9 Hz). Vanadium catalyzed directed epoxidation[14] gave epoxy alcohol **17**, which was then oxidized to epoxy ketone **10**.

With epoxy ketone **10** in hand, the α-C13 oxygen of alcohol **4** was installed via Rubottom oxidation (Scheme 6). The stereochemical outcome of the oxidation was as expected, but opposite to that obtained earlier in the Rubottom oxidation of an enone similar to **11**.[3] The α-stereochemistry was assigned on the basis of the $J_{13,14}$ coupling (12.4 Hz).

Reduction of ketone **4** with LiHAl(O-*t*-Bu)$_3$ afforded diol **18** in quantitative yield as a single stereoisomer. The C12 stereochemistry was assigned on the basis of the $J_{12,13}$ coupling (2.8 Hz). Diol **18** was converted to diacetate **19** in good yield. Ozonolysis of the alkene then afforded ketone **20**.

In planning the total synthesis of the massileunicellins, we had originally considered an approach that would employ a more highly substituted aldehyde corresponding to C2–C7 in the initial aldol reaction with (*S*)-dihydrocarvone (cf. Fig. 1 and Scheme 1). However, we were concerned that this would restrict the flexibility of the synthesis by locking in the C2–C7 fragment too early in the synthesis. We decided in favor of a more flexible strategy that would involve a carbonyl addition to install the 3° C3 stereocenter and the C2–C7 fragment. We recognized that a chelation controlled addition to the C3 methyl ketone **20** might afford the requisite C3 stereochemistry.

There are scattered reports of chelation controlled additions of carbon nucleophiles to monocyclic and polycyclic 2-acyl-tetrahydrofurans that proceeded with variable levels of diastereoselectivity.[5b,15] However, it was by no means obvious that a chelation controlled addition would be feasible in this context. Molecular modeling studies using the Titan® modeling program of a simplified analog of ketone **20** revealed a substantial preference for conformations with the carbonyl oxygen disposed toward the C14 isopropyl substituent (Fig. 2). Conformations that possessed a small O–C2–C3–O dihedral angle, as would be necessary in a chelate ring, were ca. 4–5 kcal/mol higher in energy due to steric

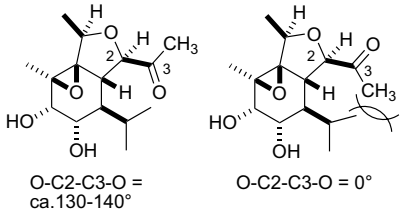
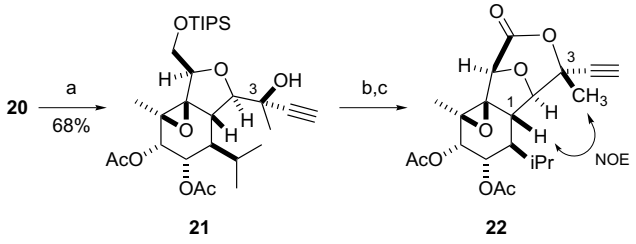


Figure 2.



Scheme 7. Reagents and conditions: (a) ethynylMgBr, Ti(O-*i*-Pr)$_4$, ether, −78 °C; (b) Bu_4NF, THF, 92%; (c) PCC, CH_2Cl_2, 45%.

interaction between the ketone methyl and the isopropyl groups. Thus it was unclear whether the requisite chelate ring would be energetically accessible.

In the event, addition of ethynylMgBr to ketone **20** using the protocol of Hirama et al.[16] afforded a single stereoisomeric alcohol **21** consistent with chelation controlled addition based on ^1H NMR analysis of the crude reaction mixture (Scheme 7).[17] For the purpose of determining the C3 stereochemistry, alcohol **21** was converted to tetracyclic lactone **22**. NOESY analysis showed cross peaks between the C3 methyl substituent and H1.[18]

In summary, we have found that an oxidative rearrangement–epoxidation of cycloaldol adduct **5** allows for the efficient installation of the C11, C12, and C13 oxygens of the massileunicellins in a stereocontrolled fashion. Chelation controlled alkynyl metal addition to the C3 methyl ketone gave the 3° alcohol with high stereoselectivity. Isobenzofuran **21** possesses eight of the nine stereocenters present in the massileunicellins. Further studies are in progress to complete the synthesis of massileunicellin D.

Acknowledgements

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