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Synthetic strategies toward the decalin motif of maklamicin and related spirotetronates†‡

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Herein we describe a scalable approach to the decalin moiety of maklamicin. Key to the synthesis is an intramolecular Diels–Alder (IMDA) reaction that proceeds *via* an *endo*-axial transition state to generate the desired stereochemistry. We explored the diastereoselectivity of the IMDA reaction as a function of both chiral catalysis and acyclic precursor stereochemistry.

Introduction

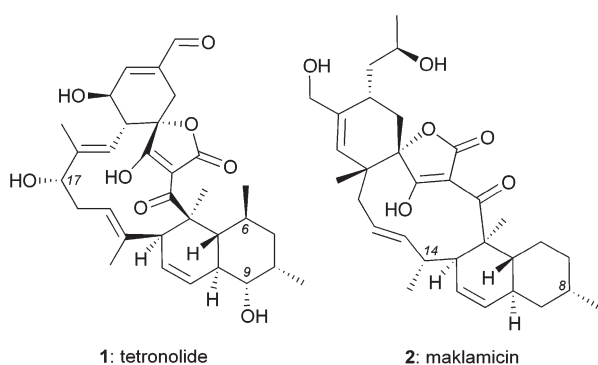
Isolated from various *Micromonospora* strains, spirotetronate polyketides constitute a peculiar family of natural products characterized by a complex chemical architecture and intriguing bioactivity as antitumor antibiotics.¹ Tetrocarcin A, the defining member of this family, contains an aglycon core, referred to as tetronolide (**1**),² that is glycosylated at the C9 and C17 centers (Fig. 1). This natural product displays promising anticancer properties *in vitro* and in animals³ that may stem from its ability to induce cell stress and inhibit Bcl-2 expression.⁴ Tetrocarcin A also exhibits potent cytotoxicity against several Gram-positive bacteria (*e.g.* MIC: 0.38 μ M

against *Bacillus subtilis*).^{3b,5} Interestingly, it has been shown that glycosylation of C9 is essential for antimicrobial activity but inconsequential for anticancer activity.^{5c,6} The influence of glycosylation to the antimicrobial potency has also been observed in other spirotetronates.^{5c,6,7}

The biological and pharmacological potential of spirotetronates has fuelled efforts to isolate new family members. Along these lines, Igarashi *et al.* reported the isolation of maklamicin (**2**) from *Micromonospora* sp. GMKU326.⁸ This novel spirotetronate was shown to exhibit both antimicrobial activities against various Gram-positive bacteria (*e.g.* MIC: 0.30 μ M against *Bacillus subtilis*) and anticancer activities (IC₅₀: 17–34 μ M against various cancer cells lines).⁸ Intriguingly, maklamicin exhibits potent antimicrobial activity in the absence of C9 glycosylation, which is essential for other spirotetronate polyketides.^{5c,6,7}

Structurally, maklamicin (**2**) encapsulates a *trans*-decalin and a spiro-tetronic acid moieties within a strained 11-membered macrocyclic motif.^{8,9} Herein we describe synthetic approaches towards the decalin moiety of **2**.

Inspired by the biosynthetic pathway of spirotetronates, we envisioned that the decalin moiety of maklamicin would arise from an intramolecular Diels–Alder reaction (IMDA).¹⁰ This strategy has been successfully applied to the synthesis of related natural products.^{11,12} Closer analysis of this IMDA reveals four possible transition states that give rise to four distinct decalin diastereomers (Fig. 2). The two *endo* transition states derive from the relative orientation of the C8 methyl group during the transition state of the IMDA reaction that influences the facial selectivity of this cycloaddition. Based on the C8 methyl group orientation, we define these transition states as *endo*-equatorial and *endo*-axial.¹³ In a similar fashion, depending on the C8 methyl group orientation, we can have the *exo*-equatorial and *exo*-axial transition states (Fig. 2). To obtain the desired stereochemistry of the maklamicin decalin unit (*i.e.* compound **5**), the IMDA should proceed *via* an

Fig. 1 Structures of tetronolide (**1**) and maklamicin (**2**).^aDepartment of Chemistry & Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA. E-mail: etheodor@ucsd.edu^bDepartment of Chemistry, South University of Science and Technology of China, Shenzhen, Guangdong 518055, China. E-mail: xuj@sustc.edu.cn

†Dedicated to Professor Ei-ichi Negishi on the occasion of his 80th Birthday.

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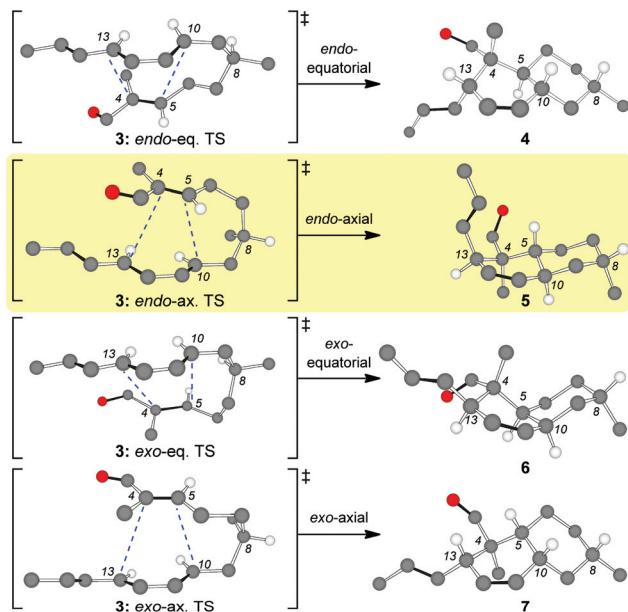
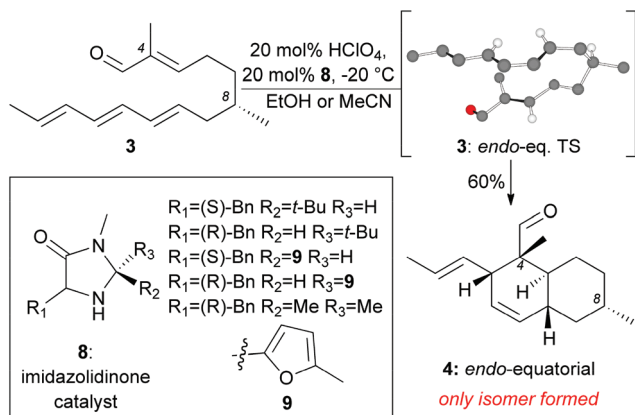


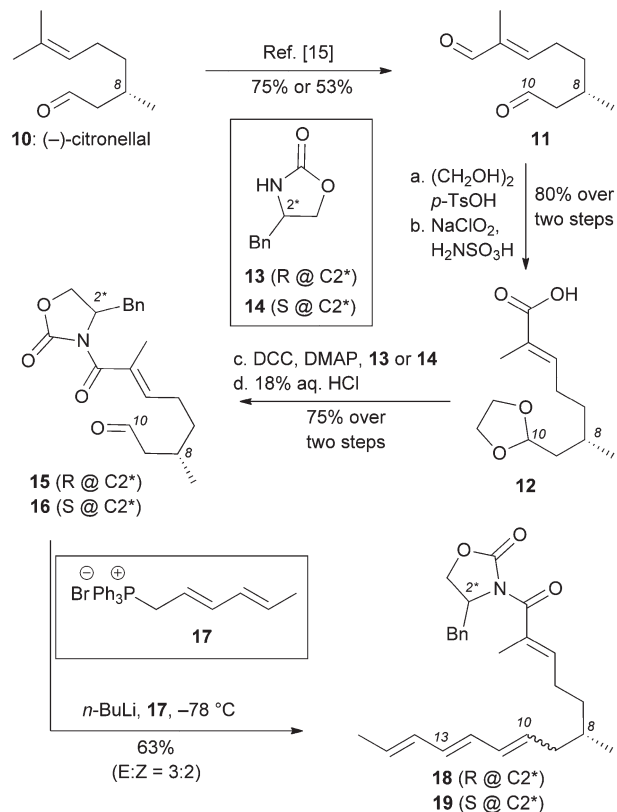
Fig. 2 Possible transition states for the IMDA of compound **3** (only selected hydrogens are shown). The terms axial and equatorial refer to the relative orientation of the C8 methyl group.

endo-axial transition state (**3: endo-ax. TS**). Published reports indicate that the facial selectivity of this type of an IMDA is expected to proceed *via* an *endo-equatorial* transition state (**3: endo-eq. TS**).¹⁴ With this in mind, we sought to explore various methods that could alter the facial selectivity of the IMDA in favor of that encountered in the structure of maklamicin.

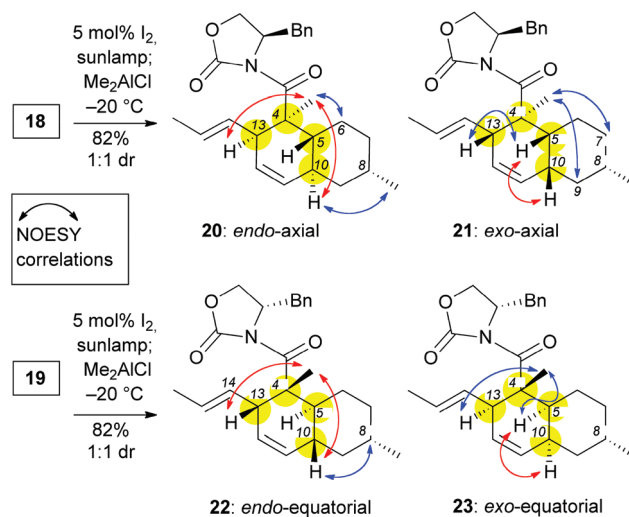
Our model studies toward the synthesis of the maklamicin decalin core are highlighted in Scheme 1–3. Previously, we demonstrated that triene **3**, synthetically available from (–)-citronellal (**10**) in 3 steps, undergoes an IMDA in the presence of Et₂AlCl at –78 °C to produce the *endo-equatorial* product **4**.¹⁵ We hypothesized that an organocatalytic process could overcome the inherent substrate selectivity of this system and favor construction of cycloadduct **5**, the one encountered in the structure of maklamicin. These studies are



Scheme 1 Studies on the IMDA of **3** under imidazolidinone organocatalysis.



Scheme 2 Synthesis of polyenes **18** and **19** containing benzyl oxazolidinones as chiral auxiliaries.



Scheme 3 Products obtained from an IMDA reaction of **18** and **19**.

summarized in Scheme 1. We performed this reaction in the presence of various imidazolidinone catalysts **8** under previously optimized conditions (20 mol% HClO₄, 20 mol% catalyst, MeCN or EtOH, –20 °C).^{12c,16} Under these conditions, the IMDA reaction was slow (3 days for completion) and produced exclusively the *endo-equatorial* adduct **4**.¹⁵ The results indicate that the catalysis was not effective in our substrate, presumably

due to the presence of the C4 methyl group adjacent to the carbonyl group. This methyl group likely prevents the transiently formed iminium intermediate from assuming the geometry needed for the desired facial selectivity of IMDA, thus diminishing the ability of the catalyst to direct the stereochemical outcome of this reaction.^{16,17}

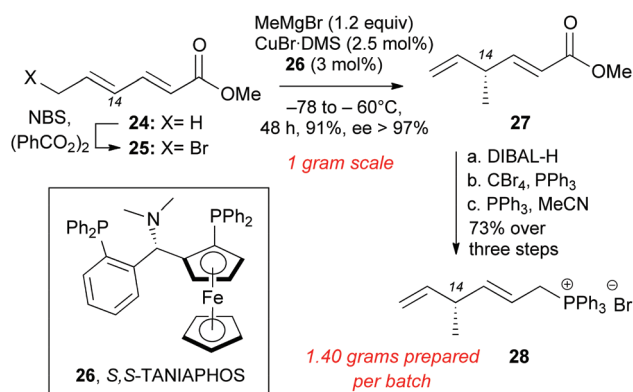
In light of these results, we pursued an alternative strategy, shown in Scheme 2, in which the desired facial stereoselectivity of IMDA could be achieved using Evans oxazolidinones (e.g. compounds **13** and **14**) as chiral auxiliaries.¹⁸ The modified strategy departed from (*S*)-(-)-citronellal (**10**) that, following established protocols, was converted to enal **11**.^{15,19} The difference in the chemoselectivity between the two carbonyl groups of **11**, allowed selective protection of aliphatic aldehyde with ethylene glycol and tosylic acid. The resulting acetal underwent Pinnick oxidation to afford the corresponding carboxylic acid **12** (80% yield over two steps). DCC coupling of **12** with (*R*)-4-benzyl oxazolidinone or (*S*)-4-benzyl oxazolidinone followed by acetal deprotection (18% aqueous HCl) yielded aldehydes **15** and **16** (75% yield over two steps). Olefination of aldehyde **15** and **16** with a Wittig ylide, produced *in situ* from phosphonium salt **17** with *n*-BuLi, afforded trienes **18** and **19** respectively in about 60% yield. The selectivity of this olefination was moderate (*E*:*Z* = ~3:2) and could not be improved using related olefination techniques.

The (*E,E*) stereochemistry of the C10 and C13 diene is essential for the desired IMDA. With this in mind, a photoisomerization of **18** and **19** was conducted with 5 mol% of iodine in dichloromethane under sun-lamp photoirradiation,²⁰ to produce almost exclusively the *E,E*-alkenes (Scheme 3). For characterization purposes, these compounds can be isolated after the photoisomerization reaction (see ESI†). Nonetheless, these polyenes can undergo the IMDA reaction in one pot, immediately after the photoisomerization. To this end, polyenes **18** and **19** were each treated with 1.1 eq. of Me₂AlCl at -78 °C and then the reaction was allowed to warm to -20 °C. Each of these reactions produced two readily separable cycloadducts in a 1:1 isolated yield. NOESY experiments were performed to assign the relative stereochemistry of these compounds (Scheme 3). In compounds **20** and **22** we observed key correlations between the C4 methyl and both protons at C10 and C13 (marked with red arrows in Scheme 3). These correlations, together with the absence of a signal between the C10 and the C5 protons indicate the presence of a *trans*-decalin ring and thus an *endo* IMDA reaction. Compound **20** also displayed NOESY correlations between (a) the C10 proton and C8 methyl; and (b) the C4 methyl and C6_{axial} proton (marked with blue arrows in Scheme 3) supporting the notion that the IMDA proceeded through an *endo*-axial transition state. This assignment is consistent with the NOESY data reported for the decalin moiety of maklamicin.⁸ In addition to the key correlations of an *endo* adduct (marked with red arrows in Scheme 3), compound **22** displayed NOESY correlation between the protons at C10 and C8 supporting the assignment of the *endo*-equatorial adduct. Similar correlations have been observed in related equisetin derivatives.²¹ In a

similar manner, compounds **21** and **23** were identified as *exo* adducts since they displayed a NOESY signal between the protons at C10 and C5 as expected in a *cis*-decalin motif (marked with a red arrow in Scheme 3). Compound **21** displayed additional correlations between: (a) the C4 methyl and protons at C7_{axial} and C9_{axial}; and (b) protons at C13 and C5 (marked in blue arrows in Scheme 3). These correlations confirm that adduct **21** was produced *via* an *exo*-axial IMDA transition state. Similar correlations have been reported for the *cis*-decalin motif of ascosalpyrrolidinone.²² On the other hand, compound **23** displayed additional correlations between the C4 methyl and protons at both C5 and C13 in support of this IMDA proceeding through an *exo*-equatorial transition state. Similar correlations have been observed in pyrrolocin B, a compound that contains a *cis*-decalin with an equatorial methyl at C8.^{21a}

The above data demonstrate that all stereoisomers of the IMDA reaction can be accessible using the chiral auxiliary approach. In the specific case of maklamicin synthesis, formation of the *endo*-axial configuration requires use of the (*R*)-4-benzyl oxazolidinone (**13**). Having established a strategy for the synthesis of the desired decalin moiety, we then turned our attention toward an appropriately functionalized acyclic precursor of the maklamicin decalin core.

Installation of the C14 methyl group at the polyene precursor of maklamicin was accomplished as highlighted in Scheme 4. Commercially available methyl sorbate (**24**) underwent allylic bromination to form **25** in 90% yield.²³ S_N2' methylation at C14 was accomplished in a stereoselective manner using Feringa's protocol that involves slow addition of **25** to a solution of methyl cuprate and *S,S*-TANIAPHOS (**26**).²⁴ Lowering the amounts of CuBr·DMS and **26** to 2.5 mol% and 3 mol% respectively, maintained the same level of enantioselectivity and afforded skipped diene **27** (91% yield, 97% ee). Due to the volatility of product **27**, its isolation yield is maximized when the alkylation reaction takes place on one-gram scale.^{24,25} The slow addition of bromosorbate (**25**) to a cold solution of the catalyst limits the scalability of this reaction. Reduction of methyl ester **27** with DIBAL-H generated the allylic alcohol, which was converted to the allylic bromide

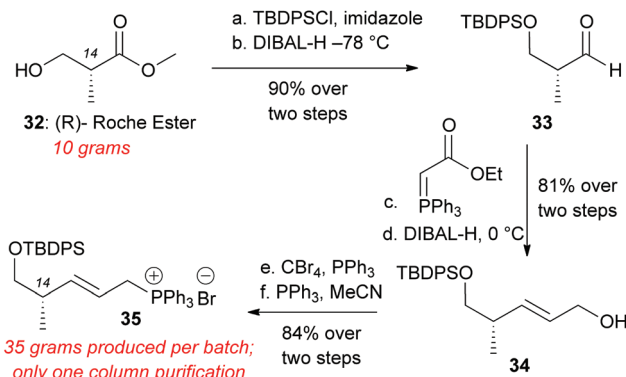


Scheme 4 Synthesis of functionalized Wittig salt **28**.

under Appel conditions.²⁶ The allylic bromide was immediately converted to the Wittig salt in MeCN and PPh₃ to produce **28** (73% over 3 steps).

Wittig olefination of aldehyde **15** with phosphonium bromide **28** yielded polyene **29** in 59% yield (*E*:*Z* = ~3:2). Double bond isomerization of this *E*:*Z* mixture was attempted but the previously established conditions promoted isomerisation of the terminal C15–C16 olefin to form the conjugated triene. Thus, the *E*:*Z* mixture was subjected to the IMDA reaction that proceeded by adding 5 equivalents of Me₂AlCl. Under these conditions we isolated cycloadduct **30** in 42% yield (formed from the *E*-isomer). Not surprisingly, the *Z*-isomer does not undergo cycloaddition under these conditions.²⁷ NOESY correlation of **30** was compared with compounds **20**–**23** to confirm that the IMDA proceeded *via* an *endo*-axial transition state. Reduction of oxazolidinone **30** with DIBAL-H followed by oxidation of the resulting alcohol with Dess-Martin periodinane yielded decalin aldehyde **31** (78% yield over 2 steps). Albeit short (9 total steps) this strategy has limited scalability due to the following reasons: (a) difficulties in installing the C14 methyl group in large scale due to limitations of the S_N2' alkylation and the cost of the catalyst; (b) inability to isomerize triene **29** to the desired all *trans* isomer; and (c) low yielding IMDA reaction that only proceeded from *E* isomer in 42% yield (Scheme 5).

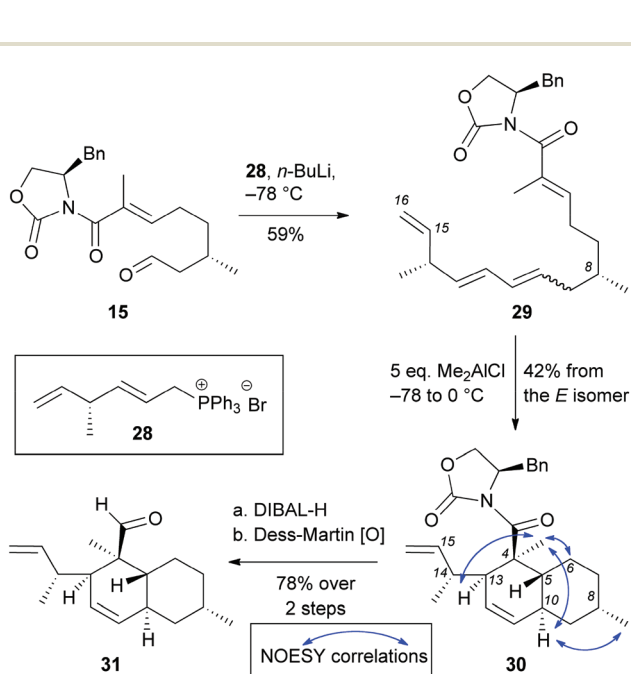
To overcome the above difficulties we sought to develop an alternative route to decalin aldehyde starting from commercially available methyl (*R*)-(-)-3-hydroxyisobutyrate (Roche's ester) (Scheme 6). This compound was protected with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in DMF in quantitative yield.²⁸ Reduction of the methyl ester to aldehyde **33** was achieved with DIBAL-H administered *via* syringe pump at –78 °C. Aldehyde **33** was directly subjected to Wittig olefina-



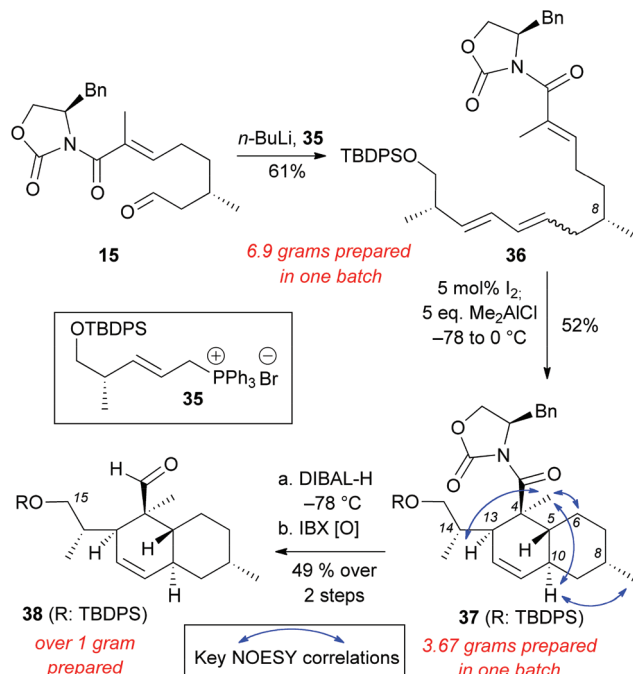
Scheme 6 Synthesis of Wittig salt **35**.

tion with (carbethoxymethylene) triphenylphosphorane. The resultant ethyl ester was reduced to the allylic alcohol **34** with DIBAL-H at 0 °C in 81% yield over two steps.²⁸ Appel bromination yielded allylic bromide, which was immediately subjected to PPh₃ in MeCN to generate Wittig salt **35** (84% over two steps). The overall preparation of this Wittig salt is high yielding, scalable, and only requires one silica column chromatography after TBDPS protection to produce over 30 grams of Wittig salt **35**.

Wittig salt **35** was treated with *n*-BuLi to generate the ylide *in situ* and then aldehyde **15** was added to form polyene **36** (61% yield, *E*:*Z* = ~3:2) (Scheme 7). The double bond isomerization and the subsequent IMDA proceeded smoothly to generate decalin **37** (52% yield on more than 3 grams scale). NOESY correlations of **37** were compared to compounds **20**–**23**, **30**, and maklamycin to confirm that the desired stereo-



Scheme 5 Synthesis of decalin **31**.



Scheme 7 Synthesis of scalable decalin moiety **38**.

chemistry was achieved.⁸ Reduction of **37** with DIBAL-H followed by IBX oxidation yielded aldehyde **38** (49% yield, 2 steps). The C15 silylated alcohol in **38** allows further derivatization (e.g. olefination protocols) en route to the chemical synthesis of maklamicin.

Conclusions

We have explored the stereochemical outcome of an intramolecular Diels–Alder (IMDA) cycloaddition as a function of the stereochemistry of the acyclic precursor. Initial studies on model systems confirmed the role of the benzyl oxazolidinone on the facial selectivity of the IMDA. We then applied this information to the synthesis of the unusual *endo*-axial decalin moiety of maklamicin. The chiral methyl groups at C8 and C14 of the IMDA precursor were introduced from enantiomerically pure starting materials. Overall, the strategy is divergent and allows access to the decalin motif **38** in 10 linear steps and good overall yield. Interestingly, decalin **38** is suitably protected for further functionalization towards the synthesis of maklamicin. Importantly, the reported studies pave the way for a general synthetic approach toward the decalin motifs of spiro-tetronates and related natural products.^{12b,21,22}

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