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A masked-alkene metathesis-based synthesis of isopulo'upone

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ABSTRACT

A metathesis-based formal synthesis of (±)-isopulo'upone has been completed featuring a masked olefin metathesis/elimination sequence followed by an intramolecular Diels–Alder reaction to construct the 5,6-fused bicyclic core.

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Olefin metathesis has rapidly emerged as one of the most versatile carbon–carbon bond forming reactions used in both organic and polymer synthesis.[1] The introduction of increasingly reactive and robust catalysts has made it routine to retrosynthetically envision using metathesis to forge any number of alkenes present in a wide range of structurally diverse compounds. Care must be taken, however, when considering metathesis reactions in polyene systems due to problems associated with chemoselectivity and/or the possibility of unwanted competing metathesis processes.[2] This has effectively limited metathesis applications in polyene synthesis to a selected number of typically sterically[3] and/or electronically[4] biased arrays. An alternative solution is to 'mask' one or more alkenes as an alkene-precursor, that is, inert to metathesis to be revealed post-metathesis (Fig. 1).[5]

Our group has been investigating the use of β-acyloxysulfones, well known intermediates in the Julia-Lythgoe olefination,[6] as suitably masked alkenes that allow for a metathesis approach to polyene systems difficult to obtain using standard metathesis technology. Recently we described an acyloxysulfone cross-metathesis/reductive-elimination reaction sequence for the preparation of 1,6- and 1,7-dienes, compounds that are particularly challenging to prepare due to a competing rapid ring closure.[7] It was anticipated that this general strategy could be extended to the synthesis of triene subunits. Specifically, compounds of type **1** were expected to undergo chemoselective cross-metathesis reactions,[8] the extent of selectivity presumably dependent on the nature of R_1 and R_2 (Scheme 1).[9] Post-metathesis reductive elimination of the acyloxysulfone would then afford trienes of type **2**.

To test this, several dienyl-acyloxysulfones were prepared by the addition of the lithium anion of sulfone **3**[10] to an appropriate aldehyde (Scheme 2). Acylation with either acetyl- or benzoylchloride gave the corresponding acetyloxy- and benzoyloxysulfones **4–7,** respectively.

As outlined in Table 1, a chemoselective cross-metathesis reaction could be achieved for each of the substrates using the Grubbs' second-generation catalyst (**8**)[11] in the presence of *cis*-1,4-diacetoxy-2-butene (Scheme 3). Reductive elimination using either Na/Hg or SmI_2[12] then completed our metathesis approach to the all-*trans* 1,3,8-trienes **9–12**. In general, for $R_1 \neq H$ (entries **4–6**) metathesis was only observed at the monosubstituted alkene irrespective of the nature of R_2. Both elimination protocols afforded the corresponding triene product in comparable yield (compare entries for **4b**). When $R_1 = H$ (**7**), at elevated temperatures a mixture of products was obtained that included the *bis*-metathesis adduct **13**. Larger amounts of **13** were observed from the reaction of the acetyloxysulfone ($R_2 = CH_3$) derivative, the larger benzoyl group ($R_2 = Ph$) presumably affording greater steric deactivation of the proximal olefin.[13] Lowering the reaction temperature and using benzoyloxysulfone **7b** promoted a chemoselective metathesis reaction affording upon reductive elimination triene **12**. It should be noted that this protocol allows for the introduction of base-sensitive functionality that would otherwise not be tolerated using standard Julia olefination conditions.[14]

1,3,8-Trienes represent important intramolecular Diels–Alder (IMDA) substrates used to generate a variety of fused-5,6-bicyclic systems.[15] As a demonstration of the utility of this sequence in the context of natural product synthesis, we set out to prepare isopulo'upone (**14**),[16] a marine toxin isolated in 1993 from mollusks *Navanax inermis* and *Bulla Gouldiana* that has attracted

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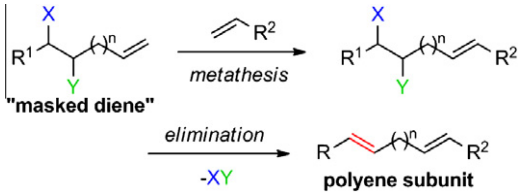
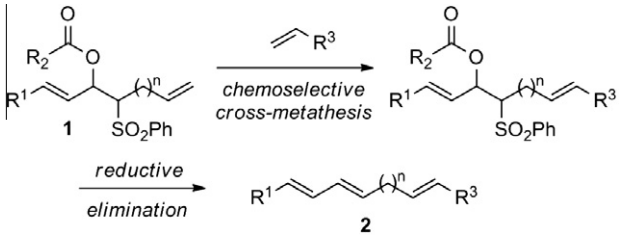
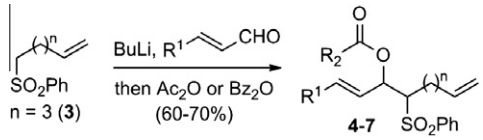


Figure 1. Masked-alkene metathesis.



Scheme 1. Masked-alkene metathesis triene synthesis.



Scheme 2. Masked triene substrate synthesis.

Table 1
1,3,8-Triene synthesis via Scheme 3

Entry	R^1	R^2	Metathesis	Elimination	Yield[a]	(**9**–**12**:**13**)[b]
4a	Ph	CH_3	A	C	74	>10:1
4b	Ph	Ph	A	D	68	>10:1
4b	Ph	Ph	A	C	72	>10:1
5a	*n*-Pent	CH_3	A	C	83	>10:1
5b	*n*-Pent	Ph	A	D	64	>10:1
6a	CH_3	CH_3	A	C	80	>10:1
6b	CH_3	Ph	A	D	70	>10:1
7a	H	CH_3	A	C	74	65:35
7b	H	Ph	A	D	67	83:17
7b	H	Ph	B	D	65	>10:1

Metathesis A: *cis*-1,4-diacetoxy-2-butene, **8**, PhMe, 80 °C; B: *cis*-1,4-diacetoxy-2-butene, **8**, DCM, rt. *Elimination* C: Na/Hg, MeOH, rt; D: SmI_2, DMPU, −78 °C.
[a] Isolated yield for two-steps.
[b] Ratios determined by ^1H NMR.

the interest of the synthetic community (Fig. 2).[17] It was thought that our acyloxysulfone metathesis/reductive elimination strategy might provide rapid entry to a triene of type **15** that could be used to construct the isopulo'upone core.

Our synthesis began from known PMB-protected aldehyde **16**[18] as outlined in Scheme 4. Addition of the lithium anion of sulfone **3** followed by acylation with benzoylchloride gave benzoyloxysulfone **17** in 64% yield as a ~1:1 mixture of diastereomers. Benzoyloxysulfone **17** underwent a highly chemoselectivecross-metathesis reaction with crotonaldehyde affording an intermediate aldehyde that was immediately treated with methylmagnesium bromide to give compound **18** as a complex mixture of stereoisomers. To complete the synthesis of **19**, it was necessary to first reductively eliminate the benzoyloxysulfone followed by oxidation of the alcohol to the desired methyl ketone. Switching the order of these steps failed to

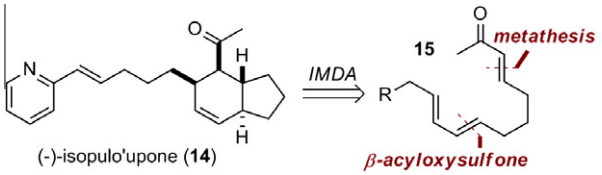
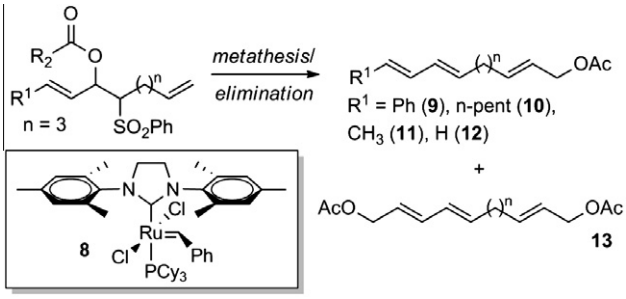
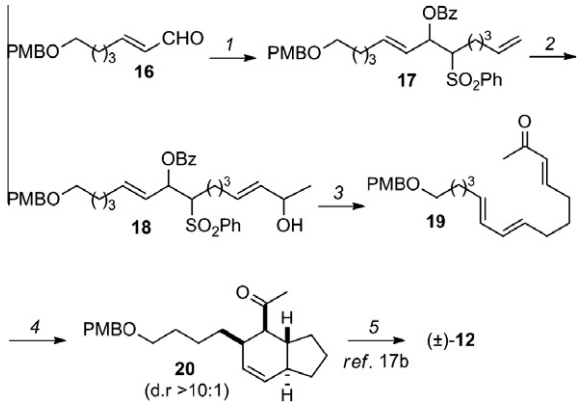


Figure 2. Isopulo'upone retrosynthesis.



Scheme 3. Chemoselective cross-metathesis.



Scheme 4. Reagents and conditions: (1) (a) **3**, BuLi, THF; (b) BzCl, pyr., DCM, 80% (two-steps); (2) crotonaldehyde, **7**, then MeMgBr, 84%; (3) (a) Na/Hg, THF/MeOH; (b) Dess-Martin [O]; (4) PhMe, 110 °C, 36% (three-steps); (5) (a) DDQ, 60%; (b) two-steps, Ref. 17b.

provide **19** as the methyl enone intermediate proved sufficiently sensitive to reductive elimination conditions. In the event, sodium–mercury mediated elimination followed by Dess–Martin oxidation gave **19** in sufficient purity that it could be taken directly into the Diels–Alder reaction without additional purification. Simply heating a solution of triene **19** in toluene to 110 °C at ambient pressure resulted in a smooth intramolecular Diels–Alder reaction, giving compound **20** with exclusive endo-selectivity as detectable by ^1H NMR.[19] Removal of the PMB-protecting group with DDQ then bisected the route previously described by Evans,[17b] the synthesis of (±)-isopulo'upone completed in three-steps from **20**.

An acyloxysulfone metathesis/elimination reaction sequence has been extended to include the synthesis of 1,3,8-trienes featuring a chemoselective cross-metathesis reaction. The acyloxysulfone served to not only mask an internal alkene thereby preventing ring-closure, but also to sterically deactivate a neighboring olefin toward metathesis. This approach allowed for the rapid assembly of the

core of the natural product isopulo'upone. Ongoing efforts are aimed at highlighting the utility of an acyloxysulfone metathesis/elimination strategy for the preparation of a range of polyene systems with applications in natural product synthesis.

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Supplementary data

Supplementary data (complete analytical data and experimental procedures for new compounds **9**–**12**, **17**, **19**, **20** are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.082.

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