Organic LETTERS

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A Short Access to the Skeleton of Elisabethin A and Formal Syntheses of Elisapterosin B and Colombiasin A

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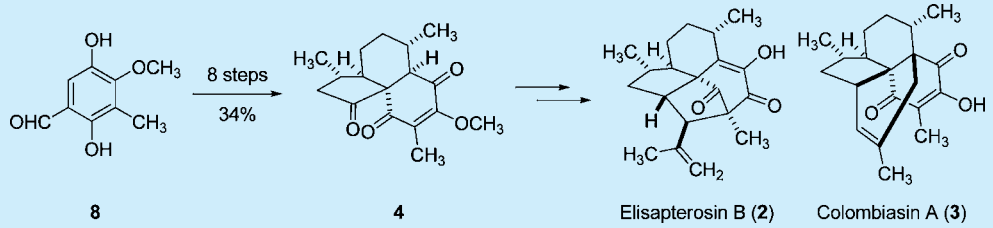
Supporting Information



ABSTRACT: A short stereoselective synthesis of the Elisabethin A skeleton **4** is described, which opens a formal access to the diterpenes Elisapterosin B and Colombiasin A as well. Key reactions were an intermolecular *endo*-selective Diels–Alder reaction to generate the decalin part of the molecule, a chemo- and diastereoselective allylation of an aldehyde with allylzinc, a palladium ene annulation of the cyclopentane ring, and a novel sulfonium ylide induced fragmentation of a polycyclic ketone. Additional insights have been gained for the crucial epimerization at C-2.

In 1998, the Rodriguez group reported the isolation and characterization of three diterpenoids with unusual structures and interesting biological activities from the West Indian sea whip *Pseudopterogorgia elisabethae*, collected in deep waters near San Andreas Island (Colombia). Appropriately, these compounds were called Elisabethin A (**1**), Elisapterosin B (**2**), and Colombiasin A (**3**) (Figure 1), and it has been postulated that they are biogenetically interconnected via Elisabethin A.[1]

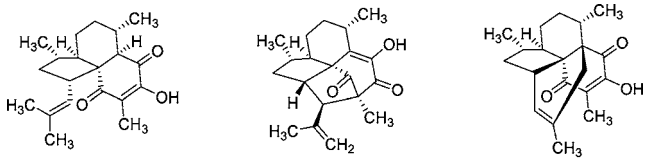
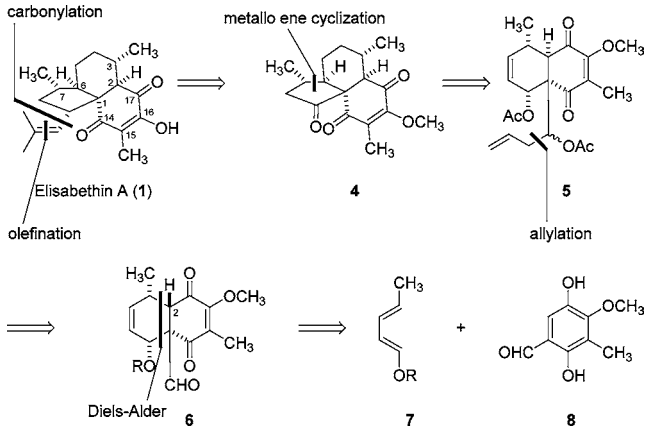


Figure 1. Structures of Elisabethin A and two related diterpenes.

2 and **3** have been frequently visited synthetic targets, due to their demanding architecture and interesting biological profile.[2] Most of these syntheses have utilized an intermolecular Diels–Alder addition to construct a decalin type intermediate first, which was then converted either into **3** via an intramolecular Diels–Alder reaction[2b−d,f,g] or into **2** via a [5 + 2]-cycloaddition.[2d,e,g] As an alternative, Harrowven et al. have prepared a bicyclic intermediate via an annulation to dihydrocarvone,[2e] and Jacobsen et al. have converted **3** directly into **2**.[2f] The Rawal group reported the asymmetric synthesis of **2** via an intramolecular Diels–Alder reaction with subsequent oxidation.[2h] Similarly fascinating is the tricyclo[7.4.0.01,5]-tridecane ring system of **1**, which features a fully substituted enedione moiety and six contiguous stereogenic centers, one of them quaternary. It is no wonder, then, that this target has also attracted significant interest among synthetic chemists.[3] About 10 years ago the Rawal group and our group published approaches to **1** via intramolecular Diels–Alder addition,[4] which due to some stereochemical assignments have met with criticism from outside.[5] This prompted us to test a different strategy, now based on intermolecular Diels–Alder cycloaddition.[6] Our retrosynthetic plan of **1** (Scheme 1) was so designed to build up the six stereocenters step by step, which should allow us to assign the configuration of every single carbon atom individually. The decalin system was to be constructed first to install the crucial quaternary center, before

Scheme 1. Retrosynthetic Plan of 1



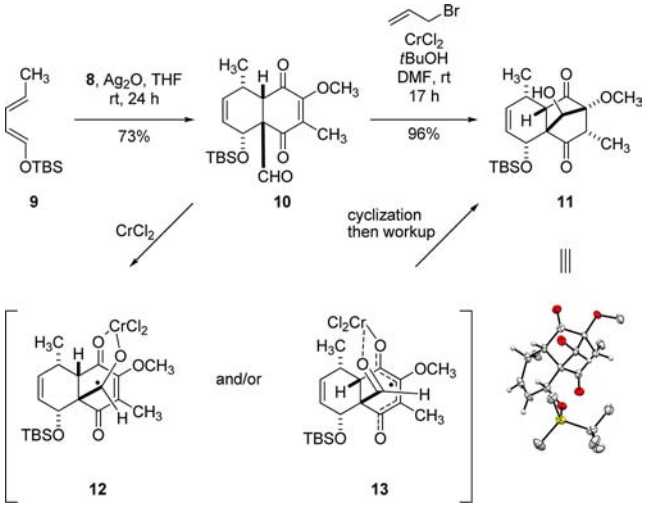
Received: July 9, 2014
Published: August 4, 2014

   dx.doi.org/10.1021/ol501998y | *Org. Lett.* 2014, 16, 4276–4279

annulating the cyclopentane ring via a Heck-type metallo-ene cyclization.[7] A particular challenge lies in the enolization/epimerization of C-2, which has been a problem in the Rawal synthesis.[4b] The last stage of the synthesis should deal with the isobutenyl side chain at C-9.

Our synthesis started with the known compounds **8** and **9**.[8] Treatment of this mixture with silver(I) oxide led to the Diels–Alder adduct **10** as a pure diastereomer.[6] In view of the presence of two additional carbonyl groups, we expected regiomeric problems for the allylation of the aldehyde. In fact, standard Grignard conditions resulted in the formation of a complex, inseparable product mixture. An iodine-catalyzed Sakurai reaction, described in the literature as a selective allylation of aldehydes,[9] afforded a complex product mixture as well. Allylation with tributylallylstannane, as well as Brown or Barbier type allylations,[10] also failed. After that the Nozaki–Hiyama–Kishi (NHK)[11] allylation was tried. With an excess of $CrCl_2$ in DMF, however, tricycle **11** was the only product in quantitative yield, and none of the desired allyl adduct had been formed. This result nicely agrees with our earlier mechanistic studies of the NHK reaction in which ketyl radical anion intermediates such as **12** and **13**[12] have been postulated (Scheme 2). Obviously, this pathway is much faster than a

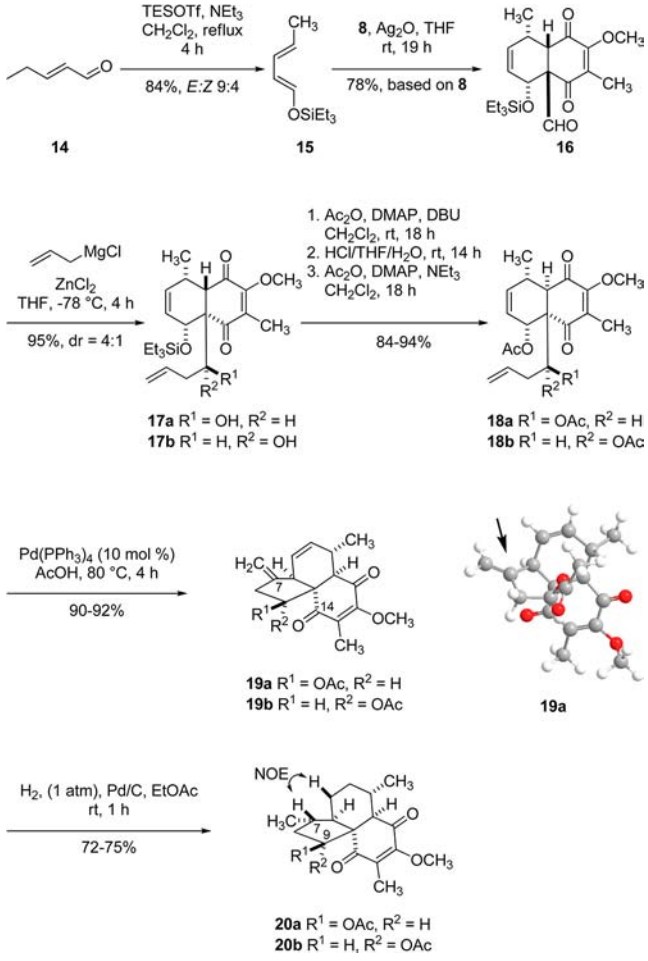
Scheme 2. Synthesis of Decalin 10 and the Formation of 11 under NHK Conditions



competing formation of the chromium allyl species and its addition to the aldehyde. The crystal structure of **11** confirmed the relative configuration of adduct **10** and, hence, the *endo* selectivity of the Diels–Alder reaction as well.

After that, we replaced the TBS group with the more labile TES ether and switched from NHK to allyzinc[10c] allylation. Hence, diene **15** was prepared from aldehyde **14** as an *E/Z* mixture containing 30–35% of the required (*E/E*)-diene. In situ treatment of aldehyde **8** with an excess of the diene mixture and silver(I) oxide led to diastereomerically pure Diels–Alder adduct **16**. Transmetalation of allylmagnesium chloride with $ZnCl_2$ and addition of the resulting zinc organyl to **16** provided an inconsequential mixture of the two diastereomeric homoallylic alcohols **17a,b** in a ratio of 4:1 and 95% yield. To facilitate NMR analysis, the epimers were separated and acetylated with acetic anhydride. *cis–trans* epimerization at C-2 with DBU, removal of the TES ether, and acetylation afforded intermediates **18a,b** in almost quantitative yield. For the annulation of the cyclopentane ring we utilized a palladium ene cyclization which was developed by Oppolzer et al.[13] in the late 1980s but has received little attention in total synthesis so far. Gratifyingly, heating of compounds **18a,b** with tetrakis(triphenylphosphine)palladium in glacial acetic acid afforded the envisaged tricycles **19a,b** in excellent yield. Hydrogenation with palladium on charcoal gave intermediates **20a,b** with the desired configuration at C-7, which was verified by NOE experiments. Although the hydrogenation of the exocyclic double bond in **19a,b** seems to occur from the more hindered, concave site of the molecule, MM2 energy minimization of a 3D model of **19a** showed that the carbonyl at C-14 adopts an axial position which directs the hydrogenation to the opposite face (Scheme 3).

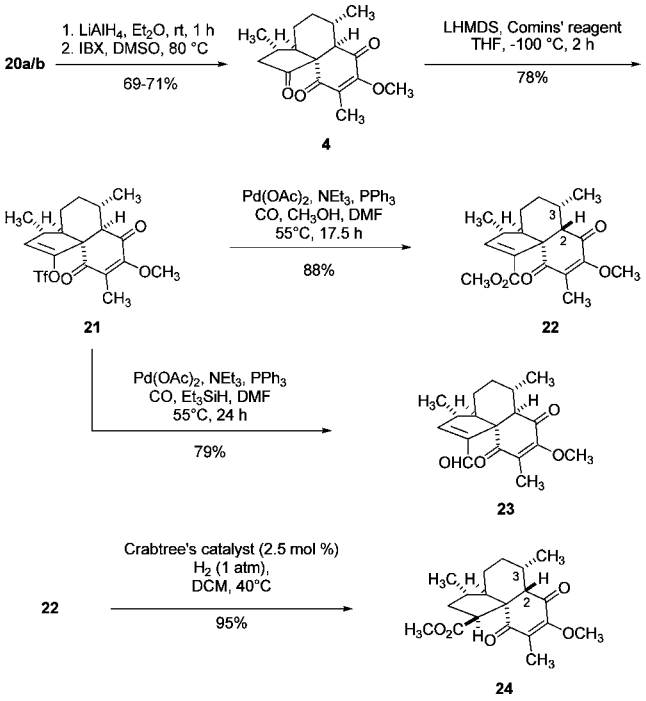
Scheme 3. Synthesis of Tricyclic Intermediate 20



Having thus established the relative configurations of five stereogenic centers in **20a,b** properly, we ventured on the elaboration of the side chain at C-9 (Scheme 4). Removal of the acetate by standard hydrolysis led to extensive decomposition. In the end, we took recourse to a global reduction of all carbonyls in **20a,b** with lithium aluminum hydride. A mixture of epimeric alcohols was formed which, without separation and purification, was reoxidized with IBX to give ketone **4** as a single product. Transformation of the keto moiety of **4** into the corresponding enol triflate **21** worked smoothly. All attempts to introduce the isobutenyl group by direct CC coupling failed. In the end, carbonylation of the triflate led to

dx.doi.org/10.1021/ol501998y | Org. Lett. 2014, 16, 4276–4279

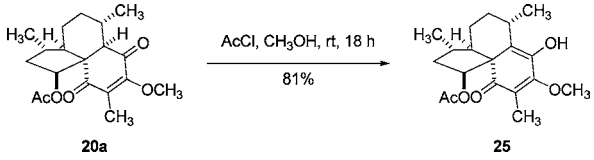
Scheme 4. Synthesis of Elisabethin A Derivatives 22–24[a]



[a]Abbreviations: IBX, 2-iodobenzoic acid; Comins' reagent, 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine; Crabtree's catalyst, (*SP*-4)-[tris(cyclohexyl)phosphane][(1,2-η:5,6-η)-cycloocta-1,5-diene]pyridineiridium(1+) hexafluoridophosphate.

ester **22**; however, this occurred under complete epimerization of H-2 from the axial to an equatorial position.[14] Interestingly, the carbonylation of **21** to aldehyde **23** proceeded without epimerization, obviously due to the absence of methanol in the reaction mixture. Similarly, when acetate **20a** was treated with HCl/methanol, the stable enol **25** was formed and the carbonyl moiety was not restored (Scheme 5). These observations

Scheme 5. Enolization of C-2

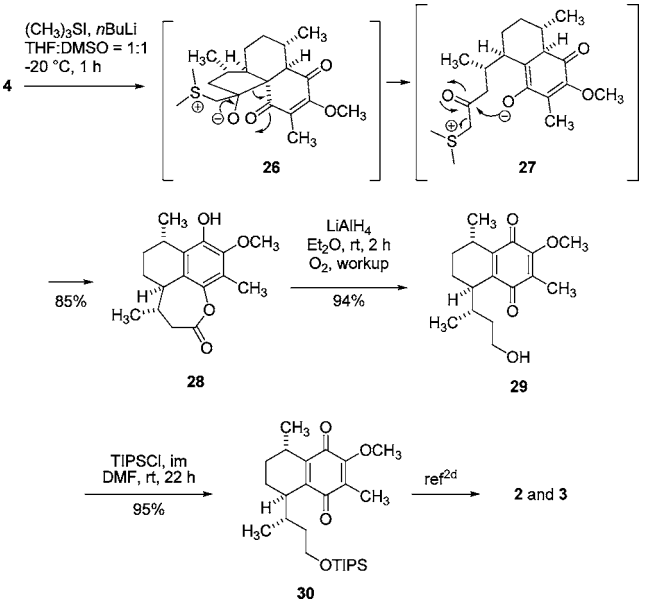


indicate that the thermodynamically favored *trans* decalin ring fusion in the bicyclic compounds **17** and **18** has been destabilized by the spiroannulation of the cyclopentane, which means that naturally occurring Elisabethin A most likely represents the thermodynamically more labile C-2 epimer.

Next, we tried to reduce the α,β-unsaturated double bond. Aldehyde **23** was inert, whereas ester **22** was hydrogenated to **24** with Crabtree's catalyst[15] and dihydrogen. Unfortunately, ester **24** proved totally inert toward any kind of C elongation, so that Elisabethin A could not be reached. Instead, we turned to the synthesis of the diterpenes **2** and **3** (Scheme 6).[2] It occurred to us that, due to the rigid geometry of the polycyclic skeleton, the C-1–C-9 bond in ketone **4** adopts a perpendicular position with respect to the cyclohexenedione ring.

Stereoelectronically this should facilitate a Grob–Eschenmoser fragmentation like retro-Claisen cleavage,[16] promoted by

Scheme 6. Retro-Claisen Cleavage of Ketone 4 and Formal Synthesis of Diterpenes 2 and 3



concomitant aromatization and considerable strain release. A number of bases were tried in vain, until we found that trimethylsulfonium methylide induced a clean conversion of **4** into lactone **28**. Presumably, a regioselective attack of trimethylsulfonium methylide onto ketone **4** affords alkoxide **26**, which undergoes a retro-Claisen reaction to form intermediate **27**. Attack of the phenolate at the α-sulfonium ketone releases trimethylsulfonium methylide and generates the seven-membered lactone **28**. LAH reduction directly afforded quinone **29** after oxidative workup (Scheme 6). TIPS protection of the primary alcohol led to **30**, whose spectral data matched the corresponding intermediate in Rychnovsky's synthesis of Elisapterosin B (**2**) and Colombiasin A (**3**).[2d] This result not only constituted a diastereocontrolled access to these compounds but also confirmed the correct relative configurations of C-3, C-6, and C-7 in intermediate **20**.

In conclusion, we have presented a rapid and stereocontrolled access to the Elisabethin A skeleton (eight steps (34%) to ketone **4**) and formal syntheses of Elisapteroside B and Colombiasin A as well. Key reactions were an intermolecular *endo*-selective Diels–Alder reaction to generate the decalin part of the molecule, a base catalyzed *trans*–*cis* epimerization at C-2, a chemoselective aldehyde allylation with allylzinc, a palladium ene annulation of the cyclopentane ring, and a sulfonium ylide induced fragmentation to generate a tricyclic phenolic lactone.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, and a CIF file giving all synthetic procedures and NMR data for the compounds prepared in this paper and crystallographic data for compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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dx.doi.org/10.1021/ol501998y | *Org. Lett.* 2014, 16, 4276–4279

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Austrian FWF (Fonds zur Förderung der Wissenschaften) is thanked for financial support (project P22180-N19). We are grateful to the following colleagues (all at the University of Vienna): Hans Peter Kaehlig, Lothar Brecker, and Susanne Felsinger, who recorded important NMR spectra and helped us with their interpretation; Alexander Roller and Vladimir Arion, who provided us with the crystal structure of compound **11**.

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(14) Characteristically, in the intermediates **4**, **18a,b**, **19a**, **20a,b**, **21**, and **23** an antiperiplanar coupling constant of $J_{2,3}$ = 9.7−12.4 Hz was found, whereas $J_{2,3}$ = 3.5−5.4 Hz in **16**, **17a,b**, **22**, and **24** indicated a synclinal arrangement.

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