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Calixanthomycin A: Asymmetric Total Synthesis and Structural Determination

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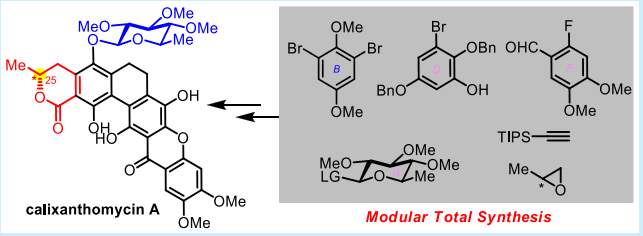
ABSTRACT: We report the first asymmetric total synthesis and structural determination of calixanthomycin A. Taking advantage of a modular strategy, a concise approach was developed to assemble the hexacyclic skeleton with both enantiomers of the lactone A ring. Stereoselective glycosylation coupled the angular hexacyclic framework with a monosaccharide fragment to produce calixanthomycin A and its stereoisomers. This enable us to determine and assign the absolute configuration of C-25 (25S) and monosaccharide (derivative of L-glucose).



Calixanthomycin A (**1**) belongs to the family of polycyclic xanthone-type natural products[1] that was isolated from cultures of *S. albus* BAC-AB1692/916/170 by Brady and co-workers in 2014.[2] Biological studies revealed that this molecule shows potent antiproliferative activity against HCT-116 cells (IC_{50} = 0.43 nM). Calixanthomycin A contains a highly oxygenated angular hexacyclic skeleton that includes a lactone A ring, a xanthone D−E−F ring, and a β-linked monosaccharide. The structure of **1** was proposed according to spectroscopic investigations, and the absolute configuration of the lactone and monosaccharide remained unestablished.[2] Interestingly, a biogenetically related polycyclic xanthone IB-00208 (**2**) was discovered by Romero and co-workers from the culture broth of *Actinomadura* sp. in 2003.[3] IB-00208 exhibits highly cytotoxic activities against several human tumor cell lines and potent antibiotic activities against several Gram-positive bacteria.[3] The structural differences between calixanthomycin A and IB-00208 mainly rely on the oxidation state of C−D ring and position of methoxy groups around the F ring.

The challenging structural features and biological potentials of polycyclic xanthones (Figure 1), such as FD-594 (**3**),[4] kibdelone C (**4**),[5] kigamicin A (**5**),[6] and arixanthomycins A−C (**6**−**8**),[7] have attracted considerable attention from the synthetic community, including the groups of Kelly,[8] Suzuki,[9] Porco,[10] Ready,[11] Martin,[12] and us.[13] We are interested in the biological functions and mechanism studies of this family of natural products, which prompted us to initiate a research program to explore its chemical synthesis.[13] In this work, we report a modular synthetic route for the asymmetric total synthesis calixanthomycin A and its stereoisomers, which enable us to determine and assign the relative stereochemistry and absolute configuration of this natural molecule.

We envisioned that a modular strategy could enable a flexible and efficient approach to prepare the stereoisomers of

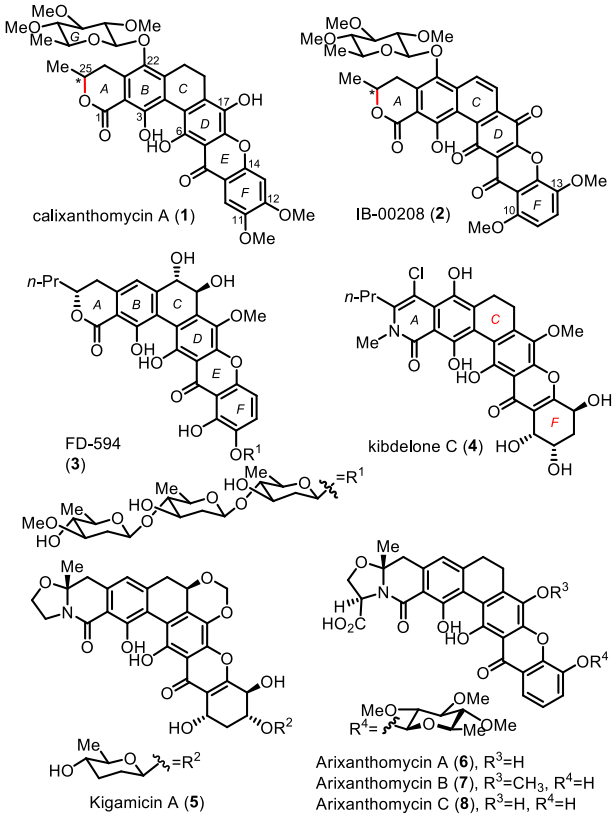


Figure 1. Structures of polycyclic xanthones.

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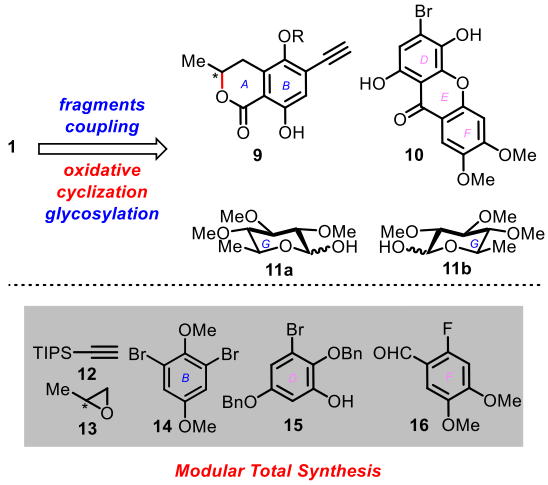
natural products and, therefore, to determine its stereochemistry (Scheme 1). Fragment coupling of **9** (two

Scheme 1. Synthetic Plan

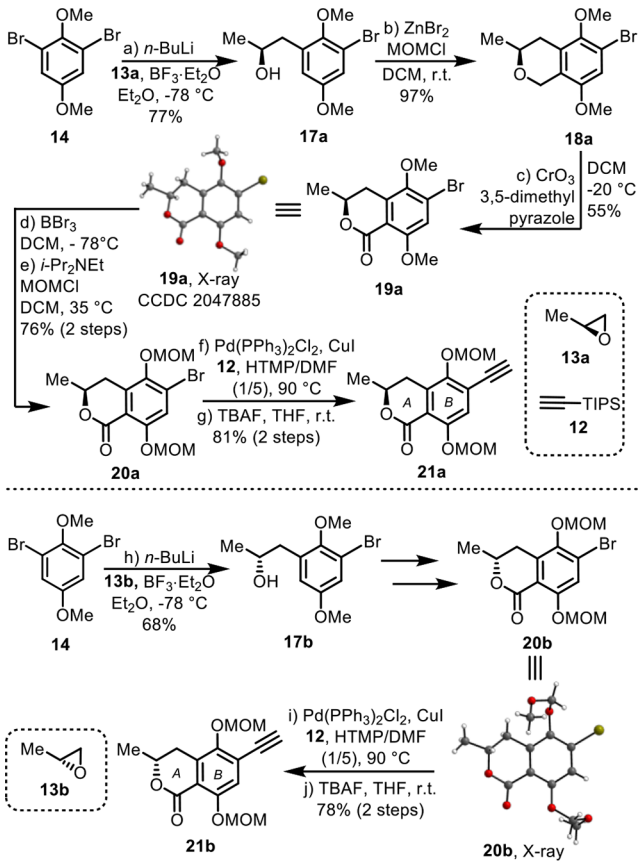


enantiomers of isochromanone A–B ring) and **10** (xanthone D–E–F ring) followed by the oxidative cyclization might furnish the angular hexacyclic framework, which could be connected with the monosaccharide **11a** or **11b** (G ring) through a late-stage glycosylation. A series of reliable reactions were designed to prepare **9** and **10** by coupling the easily available fragments **12**–**16**.

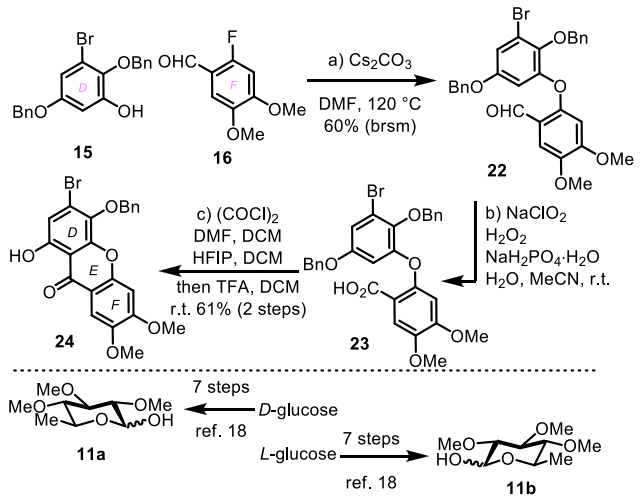
Our synthesis started from the scalable preparation of two enantiomers of the isochromanone A–B ring (Scheme 2). A known symmetric 1,3-dibromo-2,5-dimethoxybenzene **14** was selected as the starting material.[14] Treatment of **14** with *n*-BuLi gave the corresponding aromatic anion, which interacted with *S*-propylene oxide **13a** in the presence of Lewis acid (BF_3·Et_2O) to form chiral alcohol **17a** in 77% yield. Reaction of alcohol **17a** with methoxymethyl chloride (MOMCl) in the presence of $ZnBr_2$ in dichloromethane generated the benzopyran ring **18a** in perfect yield through an oxa-Pictet–Spengler cyclization.[15] Oxidation of the isochroman ring was carried out with CrO_3 under basic conditions (3,5-dimethyl pyrazole) to provide lactone **19a** in 55% yield,[12,16] and its structure and absolute configuration were confirmed by X-ray diffraction analysis. Then replacement of the methyl protecting groups of **19a** with MOM ether through a two-step sequence gave **20a**. Pd-catalyzed Sonogashira coupling of **20a** with ethynyltriisopropylsilane **12** followed by desilylation produced the terminal alkyne **21a** in 80% yield over two steps. Using the same transformations starting from **14** and *R*-propylene oxide **13b**, another enantiomer isochromanone **21b** was achieved and its absolute configuration was determined by X-ray diffraction analysis of **20b**.

The D–E–F xanthone ring was efficiently prepared from two highly functionalized benzene rings **15** (D ring) and **16** (F ring) (see details in the Supporting Information). Coupling of **15** and **16** under the basic conditions through a S_NAr reaction gave product **22**, which was oxidized to carboxylic acid **23** in good yield (Scheme 3). Following the methodology developed by Aubé,[17] 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was added to a solution of freshly prepared acyl chloride, which promoted an intramolecular Friedel–Crafts acylation to form the xanthone framework. We also developed a one-pot operation by adding trifluoroacetic acid (TFA) to the reaction

Scheme 2. Preparation of Two Enantiomers of the A–B Ring



Scheme 3. Preparation of D–E–F Ring and Two Enantiomers of Monosaccharide



mixture, which helped to selectively remove the benzyl protecting group and yielded **24** as the coupling precursor. Two enantiomers of monosaccharide **11a** and **11b** were synthesized according to a modified procedure from D- and L-glucose via a seven-step sequence, respectively (see details in the Supporting Information).[18]

With all of the coupling fragments **21**, **24**, and **11** in hand, we began to prepare the angular hexacyclic core framework (Scheme 4A). A second palladium-catalyzed Sonogashira

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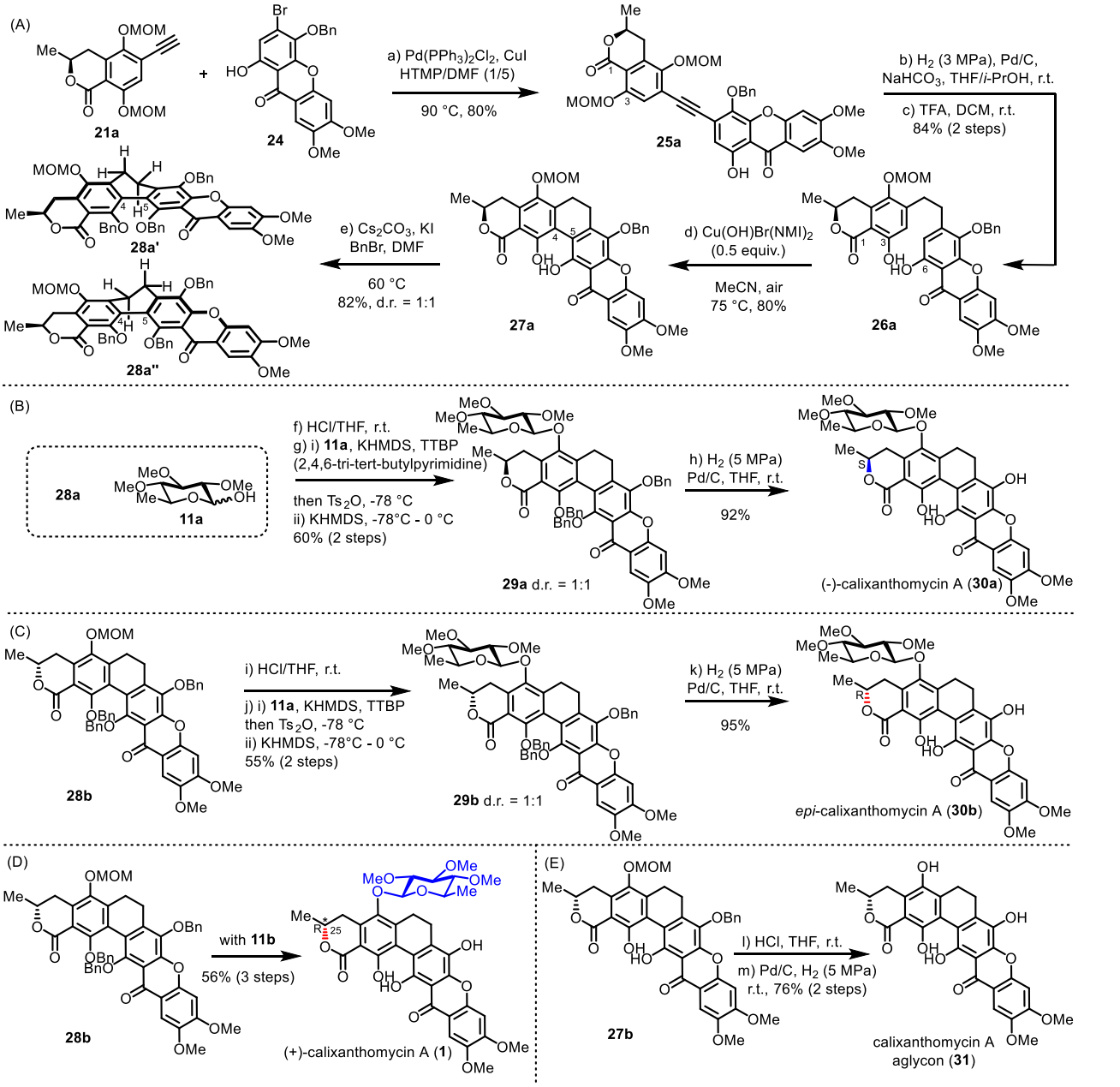
Scheme 4. Total Synthesis and Structural Determination of Calixanthomycin A



cross-coupling of fragments **21a** and **24** produced the desired coupling product **25a** in 80% yield. Pd/C-catalyzed hydrogenation of **25a** followed by selective removal of the MOM group on C3-phenol mediated by a carbonyl group on C-1 yielded the desired biphenol **26a** in 84% yield over two steps. Next, we investigated the Cu-mediated oxidative phenol coupling reactions,[19] which have been used in our previous synthetic studies of FD-594[13a] and PD-116740.[19f] Reaction of biphenol **26a** with 0.5 equiv of $Cu(OH)Br{\cdot}NMI_2$ in acetonitrile at 75 °C under an air atmosphere generated the cyclized hexacyclic skeleton **27a** in 80% yield. After protection of free phenol groups of **27a** with benzyl groups, two atropisomers **28a′** and **28a′′** were obtained as a mixture of inseparable compounds with a ratio of 1:1. We reasoned that the introduction of benzyl groups prevented the free rotation of biaryl C4−C5 bond and generated a axial chirality. Using the same transformations, hexacyclic framework **28b** (a mixture of inseparable compounds with a ratio of 1:1) was prepared from fragments *R*-**21b** and **24**.

We then turned our attention to couple the hexacyclic skeleton with the monosaccharide fragment (Scheme 4B,C). The phenolic MOM group on C-22 of **28a**/**29a** was selectively removed under acidic conditions to produce the glycosyl acceptor. Using *p*-trifluoromethanesulfonic anhydride (Tf_2O) as an activator,[20] **11a** was converted to the glycosyl tosylate species which interacted with acceptor in the presence of KHMDS to generate the desired *β*-linked glycoside **29a** and **29b** in 60% and 55% yield over two steps. Removal of three benzyl groups through the palladium-catalyzed hydrogenation (H_2, 5 MPa) afforded target **30a** and **30b** that could be used to identify and compare with the reported natural calixanthomycin A (**1**). We found that the ^1H and ^{13}C NMR spectra of our synthetic sample of **30a** were in agreement with those of the natural product (see details in the Supporting Information).[2]

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In contrast, those of synthetic **30b** and the natural product are significantly different. However, compound **30a** ($[\alpha]^{20}_D$ = −62, c = 0.01 in $CHCl_3$) holds an opposite optical rotation to the natural calixanthomycin A ($[\alpha]^{20}_D$ = +68), which revealed (−)-**30a** to be the enantiomer of natural calixanthomycin A. To further confirm this proposal, we prepare the (+)-**1** using **28b** and **11b** through the same three-step transformations (Scheme 4D). The ^1H and ^{13}C NMR spectra, high-resolution mass spectrum, and optical rotation of synthetic **1** ($[\alpha]^{20}_D$ = +51, c = 0.009 in $CHCl_3$) were consistent with the corresponding data of the natural product.[2] We thus determine and assign the absolute configuration of C-25 to be the *S*-configuration, which shares the same configuration of lactone with FD-594 (**3**) and monosaccharide to be the derivative of L-glucose. The calixanthomycin A aglycon **31** was also achieved by removal of protecting groups from **27b** (Scheme 4E).

In conclusion, we have achieved the first asymmetric total synthesis and structural determination of the polycyclic xanthone calixanthomycin A in LLS 15 steps. The modular strategy enabled us to prepare the stereoisomers of natural products efficiently to determine the stereochemistry and absolute configuration of calixanthomycin A. The existence of the derivative of L-glucose in calixanthomycin A, instead of the D-derivative, might give hints to better understand the biosynthetic pathway of this family of natural molecules. We plan to carry out the structure−activity relationship (SAR) studies of synthetic samples regarding to their anticancer activities, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00193.

Experimental procedures and characterization data (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**, **15**, **17a**, **18a**, **19a**, **20a**, **21a**, **22**, **24**, **25a**, **26a**, **27a**, **28a**, **28b**, **29a**, **29b**, **30b**, and **31** (ZIP)

Accession Codes

CCDC 2047885−2047886 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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