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Atroposelective Synthesis of Isoriccardin C through a C–H Activated Heck Type Macrocyclization

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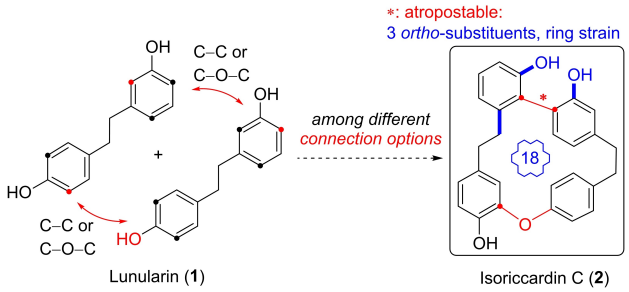
Macrocyclization is typically the key step in syntheses of cyclophane-type natural products. Considering compounds with axially chiral biaryl moieties, the control of atroposelectivity is essential for biological activity and is synthetically challenging. Herein we report on atroposelective macrocyclization involving an oxidative Heck type process and enabling the first atropo-enantiopure synthesis of isoriccardin C. A chiral sulfinyl auxiliary in the ortho-position of a biaryl axis (still flexible) was used to induce a C–H activated atropodiastereoselective oxidative Heck coupling (>98% de). The traceless character of the sulfinyl auxiliary enables the introduction of a hydroxy group to give the target molecule with >98% ee as well.

Introduction

Cyclophanes, which are constrained macrocycles with bridged aromatic rings as well as aliphatic units, are an interesting source of curiosity for organic chemists.[1] Regarding the synthesis of these intriguing molecules, the formation of the macrocycle is the most decisive step due to the rigidity of the ring structure.[2] Among macrocyclic natural products, cyclic bisbibenzyls which were isolated commonly from liverworts[3] possess many interesting biological activities such as anti-inflammatory, anti-diuretic, antifungal or antitumoral.[4] These scaffolds are biosynthetically derived from the linear "bibenzyl" lunularin (**1**) through biaryl (C–C) and/or biaryl ether (C–O–C) formation with different possible connections (Scheme 1).[5]

Within this family, isoriccardin C (**2**), an 18-membered ring macrocycle, was isolated inter alia from *Marchantia polymorpha*, *M. palmata*[6] and *M. Paleacea*[7] and various biological activities



Scheme 1. Biosynthesis and atropisomerism of isoriccardin C **2**.

of **2** were intensively studied.[8] More recently, an enantioenriched form of **2**[9] was detected in *Reboulia hemisphaerica*. The presence of a configurationally stable chiral axis was already detected before through our racemic synthesis,[10] and confirmed by Lou[9] with a computed rotational barrier of 129 kJ/mol. Moreover, the quantum-chemical CD calculations were improved by us at a higher level[11] resulting in a configurational assignment of the two atropisomers of **2** (Figure 1). From this data, we could conclude that the biaryl axis affords atropostable enantiomers (*P*/*M*) due to the presence of the three *ortho*-substituents and the ring tension of the entire molecule. It should be noted that atropostability of biaryl axes with only three *ortho*-substituents still depends on their bulkiness and more specifically, hydroxyl groups belong to the smaller ones.[12]

From a synthetic point of view, different methods for the macrocyclization key step were employed for the racemic total syntheses of these macrocyclic bisbibenzyls, respectively Wittig or HWE olefination, oxidative Wurtz, reductive McMurry and Suzuki-Miyaura couplings.[13] More precisely, racemic isoriccardin C (**2**) was synthesized by our group through a final Wittig type macrocyclization (Scheme 2a).[14]

Atroposelective methods towards cyclic bisbibenzyls remain underdeveloped mainly because of the macrocyclic strain of the biaryl molecule.[15] Remarkably, two different atroposelective strategies to access isoplagiochin D (**3**) bearing two biaryl moieties have been reported so far. We developed a chiral sulfinyl group induced diastereoselective Heck macrocyclization of the iodide **A** with high yield (80%) and diastereoselectivity (>98% de) enabling the total synthesis of enantiopure isoplagiochin D (Scheme 2b).[16] More recently, Gu and Xi reported a Pd-catalyzed macrocyclization involving a benzyl chloride and a carbene generated from a *N*-tosyl hydrazone precursor **B** (Scheme 2c). The ligand WingPhos together with

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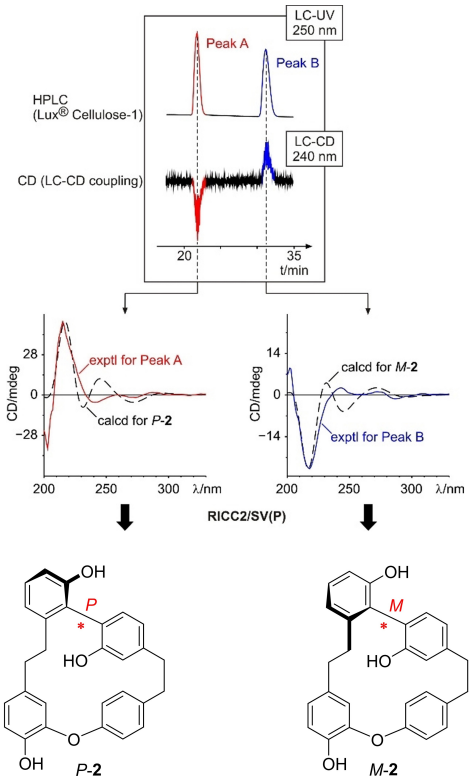


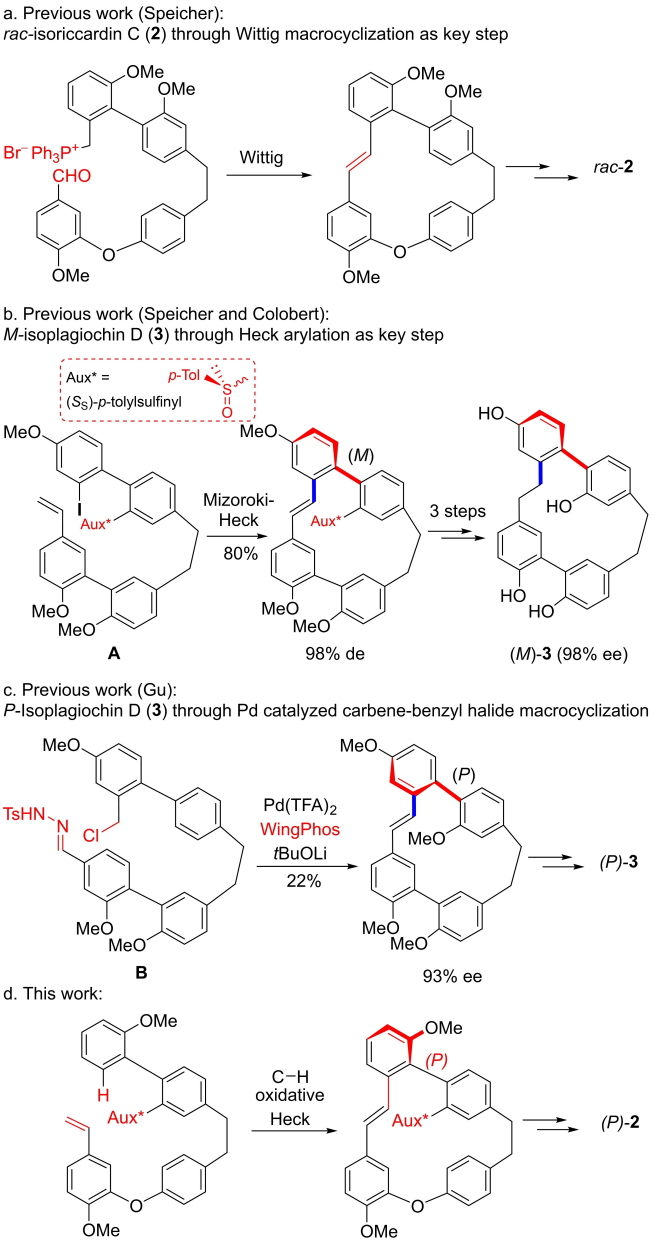
Figure 1. HPLC-CD coupling and configurational assignment through high-level quantum-chemical CD calculations for isoriccardin C **2**.[11]

$Pd(TFA)_2$ as pre-catalyst displayed a stereoselective activity giving rise to the precursor of isoplagiochin D with up to 22% yield and 93% ee.[17] However, to the best of our knowledge, no atroposelective syntheses of bisbibenzyls bearing a biaryl as well as a biarylether scaffold have been reported yet.

Results and Discussion

Therefore, and to progress we now envisaged a Fujiwara Moritani (oxidative Heck) reaction[18] using an atroposelective option developed by us[19] for the challenging macrocyclization step towards isoriccardin C (**2**) (Scheme 2d). We report on the realization of this strategy involving an asymmetric direct C–H activation, using an enantiopure sulfoxide as both directing group (DG) and chiral auxiliary. This would be the first example in literature in which the macrocycle is formed during a C–H activation process.

As chiral auxiliary and DG, our choice was turned to a chiral sulfinyl moiety which presents major advantages: (a) inexpensive access and easy preparation in an enantiopure form, (b) excellent ability for metal coordination, particularly with palladium, and specially (c) efficient and manifold post functionalization. Actually, this auxiliary can be readily removed from the products under complete conservation of the chiral information at the biaryl axis by sulfoxide/lithium exchange followed by electrophilic trapping.[16,20] Thus, within the total



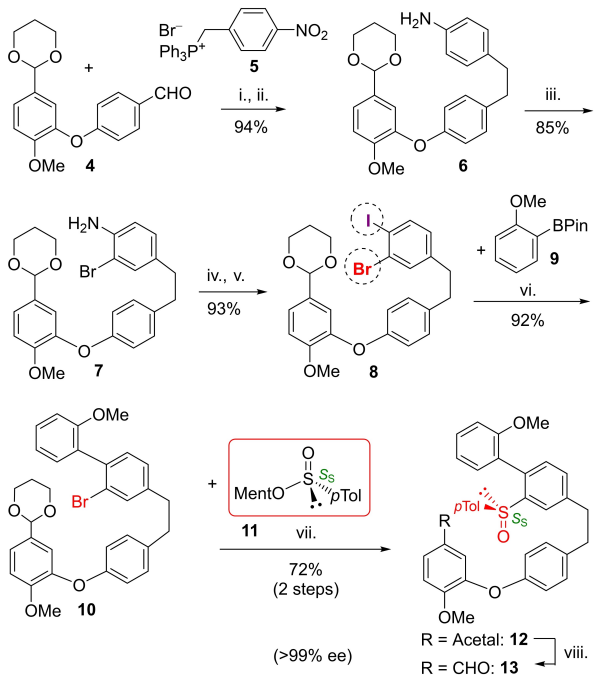
Scheme 2. Previous racemic synthesis of **2** and strategies for the atroposelective preparation of bisbibenzyls.

synthesis of isoriccardin C (**2**), the *ortho*-hydroxy group could be easily introduced by replacing the chiral sulfoxide after the macrocyclization step (Scheme 2d).

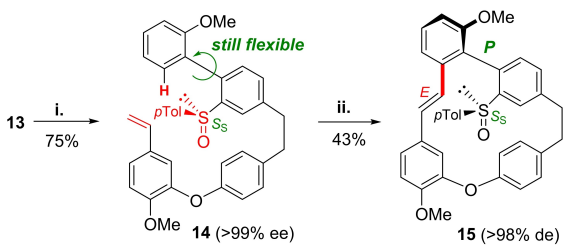
Our synthesis started with the biaryl ether **4** readily available in two steps from isovanillin (see our foregoing racemic pathway).[14] The third aromatic unit was introduced using a Wittig reaction with **5** followed by the hydrogenation of the resulting double bond to give **6**. *Ortho*-bromination led to **7** and iodination of the aniline functionality by the way of a Sandmeyer like reaction yielded the intermediate **8** bearing two halogens as possible leaving groups for the subsequent step-

by-step transformation. A fine optimization of the reaction conditions (see supp. inf.) permits the Suzuki-Miyaura cross-coupling with **9** (commercially available) providing the biaryl **10** as precursor for the introduction of the sulfinyl auxiliary. Again, through an optimization study, compound **12** is reached after a lithium bromine exchange on **10** and condensation of the aryl lithium with the enantiopure (S_S)-menthyl *p*-toluenesulfinate (**11**) at low temperature.[20] Finally, acid hydrolysis led to the desired aldehyde **13** (Scheme 3).

Starting from the aldehyde **13**, the styrene precursor **14** was then synthesized via a Wittig-reaction without loss of stereochemical purity of our chiral DG crucial for the atropodiastereoselective macrocyclization step. To our delight and after thoroughly optimized conditions, a diastereomerically pure biaryl **15** (de >98%) was obtained in good yield (Scheme 4). As



Scheme 3. Synthesis of the enantiopure tetraaryl unit **13**; i. K_2CO_3, 18-crown-6, CH_2Cl_2, reflux, 48 h; ii. H_2, 10% Pd/C, 3 bar, 5 h; iii. NBS (1.0 eq), NH_4OAc, MeCN, 0 °C, 3 h; iv. $NaNO_2$, KI, p-TosOH, MeCN, −5 °C, 15 min; v. 1,3-propanediol, triethyl orthoformate, NBu_4Br_3, 60 °C, 18 h (re-protection); vi. $Pd(PPh_3)_4$ (0.03 eq), Na_2CO_3, H_2O/EtOH/ toluene, 80 °C, 18 h; vii. 1) *t*-BuLi (2.0 eq), THF, −78 °C, 2) **11** (2.0 eq), toluene, −78 °C; viii. 2 M HCl, THF, 24 h.



Scheme 4. C–H activated oxidative Heck macrocyclization step; i. $MeP^+Ph_3Br^-$, KO*t*-Bu, THF, reflux, 18 h; ii. $Pd(OAc)_2$ (0.13 eq), AgOAc (3 eq), HFIP, DCE, 80 °C, 18 h.

expected, the chiral auxiliary exhibits excellent metal coordination and *ortho'*-directing properties during the C–H activation process but also prevents totally free rotation of the biaryl axis.[19b]

As intermediate, we postulate **16** as the favoured conformation of the transition state in which the C–H activation occurs on the opposite side of the bulky substituent of the chiral sulfoxide giving a six-members palladacycle. Thus, after activation and insertion of the palladium in the C–H bond, the sulfoxide stabilizes the formation of a six-membered palladacycle (Figure 2). Due to the bulkiness of the *p*-tolyl moiety on the upper face, the styrene moiety should approach from the less sterically hindered bottom face, the palladacycle then coordinating with the double bond. This effect is enforced by the presence of HFIP giving a hydrogen bond with the sulfinyl group. This substrate-solvent intimate interaction is supposed to modify both the coordination properties and the steric features of the chiral directing group.[19b] This intermediate leads to the formation of the *P* atropodiastereomer, which absolute configuration was clearly deduced from a single crystal structure of **15** (Figure 3).

To finalize the synthesis of isoriccardin C (**2**), the sulfinyl auxiliary was then converted into the required OH-group without loss of enantiopurity at low temperature conditions.[16] A careful three steps sequence involving the sulfoxide lithium exchange at −100 °C followed by addition of trimethoxy borane and oxidation allowed in acceptable yield the formation of compound **17** bearing the hydroxy group in *ortho*-position of the biaryl moiety (Scheme 5). Ionic hydrogenation of the stilbene bond and cleavage of the protecting methyl ethers

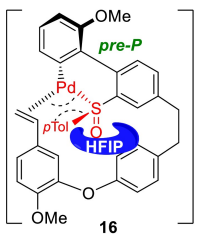


Figure 2. Proposed transition state **16** during the Heck oxidative coupling.

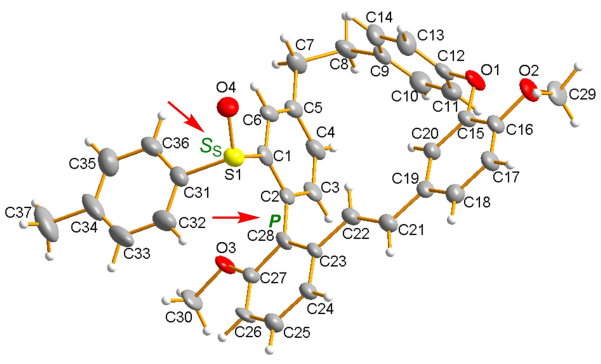
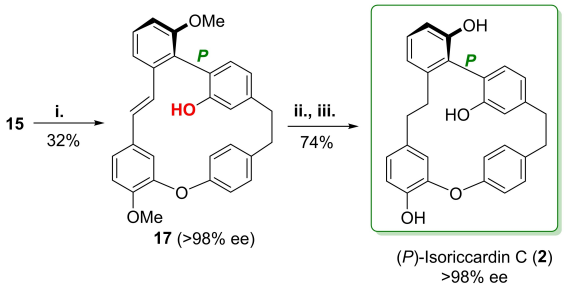


Figure 3. X Ray analysis and ORTEP structure of **15** (CSD 2054769).



Scheme 5. Completion of the synthesis for isoriccardin D (**2**); i. 1) *n*-BuLi (2.0 eq), $B(OMe)_3$ (40 eq), THF, −100 °C, 2) H_2O_2, NaOH, −100 °C to rt; ii. Et_3SiH/TFA, CH_2Cl_2, rt, 18 h; iii. BBr_3, CH_2Cl_2, 0 °C, 18 h.

afforded (*P*)-isoriccardin C (**2**) with high enantiopurity. Furthermore, and in addition to Figure 2, the configurational assignment (*P*)-**2** was confirmed by HPLC-CD analysis comparing with the previous studies[11] (see Figure 1).

Conclusions

In summary, we described the first atroposelective synthesis of isoriccardin C (2) (>98% ee for the (*P*)-atropenantiomer). The key of success is the use of an atropodiastereoselective oxidative Heck macrocyclization employing an enantiopure centrochiral sulfinyl auxiliary. The traceless character of the sulfinyl auxiliary enables the introduction of a hydroxy group into the target molecule. For the first time we applied the more atom economic C–H-activated Heck type coupling (Fujiwara-Moritani option) for the macrocyclization to give rise to a bisbibenzylic natural compound.

Deposition Number 2054769 (for **15**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Atropisomerism · Biaryls · C–H activation · Directing group · Natural cyclophanes

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