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Total synthesis of atropisomeric indolosesquiterpenoids via N–N bond formation: dixiamycins A and B†‡

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N–N dimeric indolosesquiterpene alkaloids constitute a class of under-investigated architecturally intriguing natural products. Herein, we report the first chemical oxidation approach to the asymmetric total syntheses of these atropisomeric indolosesquiterpenoids through N–N bond formation. Specifically, dixiamycins A (**1a**) and B (**1b**) were prepared through a Cu(I)-mediated aerobic dehydrogenative dimerization from the naturally occurring monomer xiamycin A methyl ester (**2b**); this preparation also represents the first total synthesis of dixiamycin A (**1a**). The monomer xiamycin A methyl ester (**2b**) was synthesized via a late-stage Buchwald Pd(II)-mediated aerobic dehydrogenative C–N bond formation.

Introduction

Pentacyclic indolosesquiterpene alkaloids (e.g., **1–3**; Fig. 1), a novel and growing class of architecturally complex secondary metabolites, were first isolated from a range of *Streptomyces* species in 2010, exhibit important biological activities such as antimicrobial, antiviral, antitumor, immunomodulatory, and enzyme inhibitory activities, and are commonly referred to as the xiamycin family of alkaloids.¹ In 2012, the atropisomeric indolosesquiterpenoid natural products dixiamycins A (**1a**) and B (**1b**) were isolated independently by Zhang and Hertweck.^{2,3} These indole alkaloids each have a rare N–N linkage that generates an important class of atropisomers, featuring axial chirality about the N–N axis where the N atoms are sp³-hybridized. Prior to this finding, the monomers of these dimers, i.e., xiamycin A (**2a**) and its methyl ester (**2b**), were isolated by Hertweck and coworkers from *Streptomyces* sp. GT2002/1503 (ref. 3a) and HKI0595,^{3b} which are endophytes from the mangrove plants *Bruguiera gymnorhiza*^{3a} and *Kandelia candel*,^{3b} respectively. Alkaloids **2a–b** have been reported to display anti-HIV and antibiotic activities.^{3a} Structurally, these alkaloids include a pentacyclic framework with four contiguous

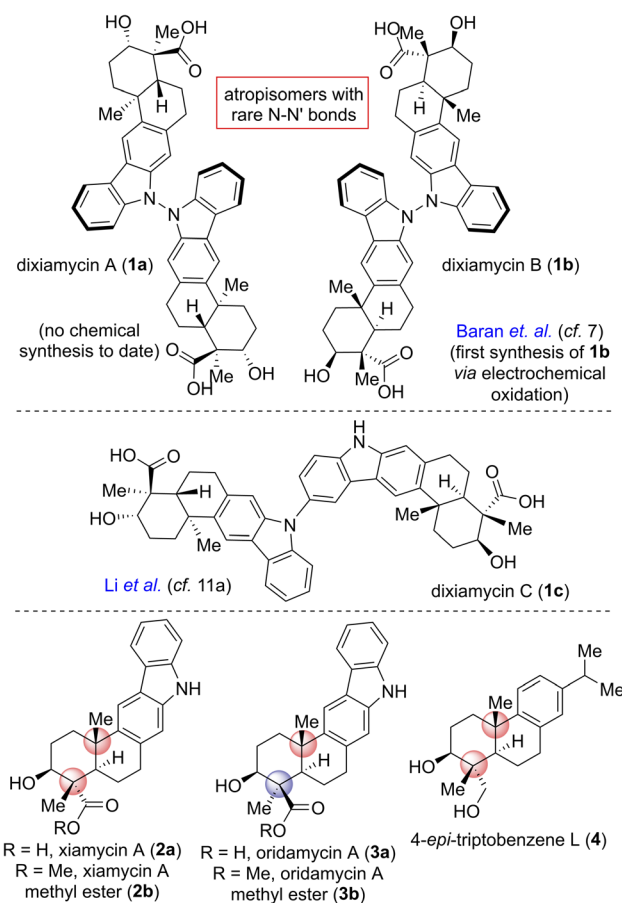


Fig. 1 Indolosesquiterpene alkaloids **1–3**.

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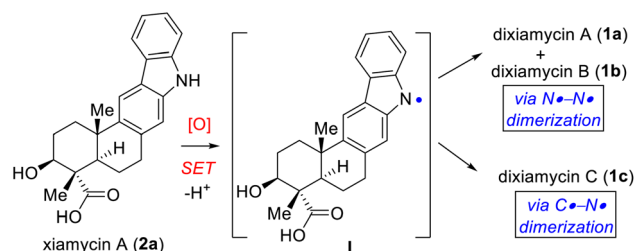
§ These authors contributed equally to this work.

stereogenic centers at the periphery of a *trans*-decalin scaffold to which is attached a carbazole unit.^{4,5} Oridamycin A (**3a**) is a diastereomer of xiamycin A (**2a**) and has been isolated from *Streptomyces* sp. KS84.^{4b}

Importantly, two out of the four stereogenic centers are synthetically challenging all-carbon quaternary centers. The new uninvestigated N–N dimeric forms of xiamycin A are nearly an order of magnitude more potent than their monomeric scaffolds.² The emerging recognition of the biological activity of these indolosesquiterpenoids has drawn considerable attention from the synthetic community, which has produced several syntheses of these alkaloids. The most efficient approach to the atropo-diastereomers of xiamycin A would be to effect a direct oxidation to form an N–N bond from the monomer as per the proposed biosynthesis following a single-electron transfer (SET) mechanism (Scheme 1). However, given that there has been rather limited success in achieving a direct N–N bond formation of two carbazole units with chemical oxidants (such as the use of stoichiometric amounts of oxidants I₂,^{6a} KMnO₄,^{6b} Ag₂O,^{6c} or dichromate^{6d}), the synthesis of dixiamycins A (**1a**) and B (**1b**), bearing sensitive functionalities, remains a formidable challenge. In this regard, an electrochemical oxidation approach reported by Baran and coworkers elegantly addressed the total synthesis of dixiamycin B (**1b**).⁷

Based on the biosynthesis proposal (Scheme 1) and a recent report on aerobic oxidation by Stahl and coworkers,⁸ we envisioned that a suitably protected xiamycin A might be made to engage, under Cu(I)-catalysis, in an oxidative N–N bond formation to provide both **1a** and **1b**. Our efforts began with identifying a practical synthesis of xiamycin A methyl ester (**2b**). Prior elegant approaches to monomeric indolosesquiterpene alkaloids have been independently developed by Baran (cyclization of a carbazole-anchored epoxy ether),⁷ Krische (TiCl₄-promoted Friedel–Crafts cyclization),⁹ Trotta (radical-induced polyene cyclization),¹⁰ Li¹¹ (6π-electrocyclization/aromatization and indole C₂–H bond activation/Heck annulation), Sarpong¹² (from (*R*)-carvone, using a photoinduced benzannulation sequence to forge the carbazole core), Dethe¹³ (oxidative Heck/aromatization for carbazole synthesis) and our group (following δCsp³–H activation of the pentacyclic skeleton of indolosesquiterpene alkaloid).¹⁴

Herein, we report the total synthesis of both N–N atropo-diastereomers of indolosesquiterpene alkaloids, namely dixiamycins A (**1a**) and B (**1b**), via a nature-inspired aerobic oxidation. Impressively, this work represents, to the best of our



Scheme 1 Biosynthesis of dixiamycins A (**1a**), B (**1b**) and C (**1c**).



Scheme 2 Hypothesized accessing of atropisomers of dixiamycins A (**1a**) and B (**1b**) and retrosynthetic plan (via 4-*epi*-triptobenzene L (**4**)).

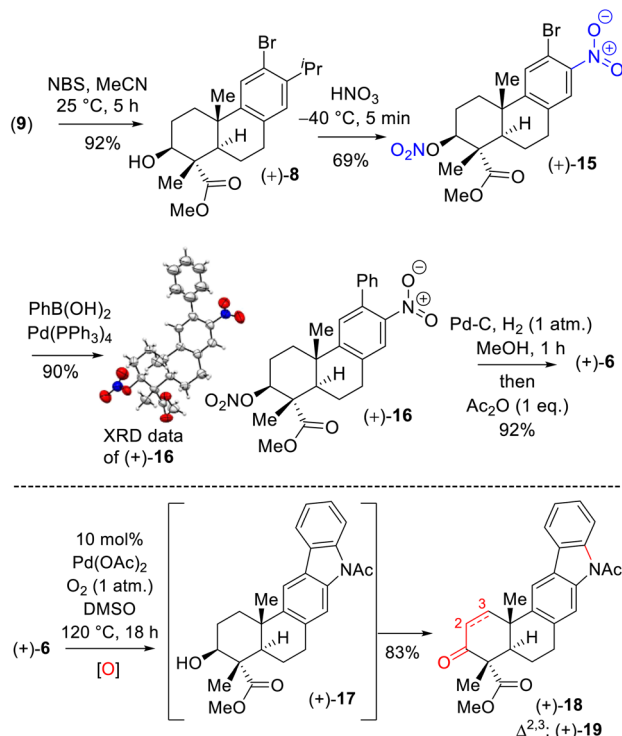
knowledge, the first total synthesis of dixiamycin A (**1a**), clearly consistent with nature's oxidative approach to dixiamycins. Moreover, the currently developed unified practical asymmetric approach to naturally occurring abietane diterpenoids (via a key epoxy-ene cyclization^{15–18}) and the congeners of the xiamycin family (via a late-stage Buchwald oxidative C–N bond formation¹⁹) would enable access to these natural products in significant quantities.

Result and discussion

On the basis of their structural similarity to naturally occurring diterpenoids, such as 4-*epi*-triptobenzene L (**4**), we envisioned a unified approach to the xiamycins (Scheme 2). Retrosynthetically, we imagined accessing highly functionalized *o*-bromo nitroarene **7** as an advanced intermediate for our synthesis. Thus, a late-stage Buchwald oxidative C–N bond formation of 2-phenyl acetanilide **6** could construct the



Scheme 3 Total syntheses of 4-*epi*-triptobenzene L (**4**) via polyene cyclization.



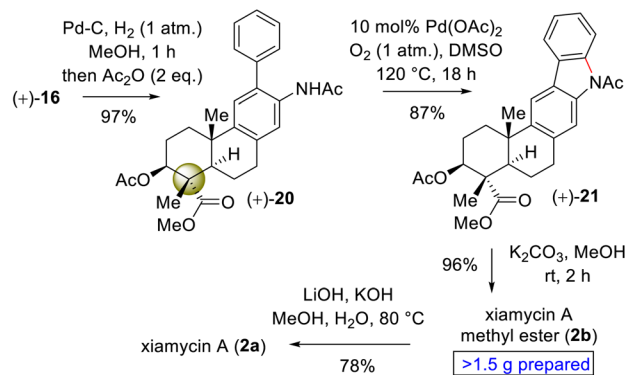
Scheme 4 Synthesis of a pentacyclic framework under oxidative C–N bond formation.



Scheme 5 Plausible mechanism involving overoxidation.

carbazole moiety of the xiamycins. *o*-Bromo nitroarene **7** could be synthesized from *o*-bromo isopropylarene **8** using an *ipso*-nitration, which in turn could be synthesized from **13** using Sharpless asymmetric epoxidation followed by Lewis-acid-assisted epoxy-ene cyclization (*via* intermediate **4**).

Our synthesis commenced with a Cu-catalyzed Csp³–Csp³ bond formation between functionalized geranyl acetate **10** and 3-isopropylbenzyl bromide **11**, followed by TBS deprotection using TBAF to access allylic alcohol **13** (Scheme 3). Sharpless



Scheme 6 Total synthesis of xiamycin A (**2a**) *via* Buchwald's oxidative C–N bond formation.

Table 1 Attempts towards oxidative N–N bond formation

Entry	Conditions	Results
1.	NaH, THF, O ₂ (1 atm) –78 °C to 25 °C	92% SM recovered
2.	O ₂ (1 atm), DCE 25 °C to 70 °C	89% SM recovered
3.	I ₂ , KI, K ₂ CO ₃ , O ₂ (1 atm) DMSO, 25 °C to 100 °C	multiple spots + 73% SM recovered
4.	PIDA, HFIP, 40 °C	decomposition + multiple spots
5.	NaI, NaIO ₄ CH ₃ CN, 25 °C	multiple spots
6.	KI, KIO ₄ CH ₃ CN, 25 °C	no conversion



asymmetric epoxidation¹⁵ of **13** with TBHP in the presence of Ti(OiPr)₄ and (+)-DET afforded epoxy-alcohol **14** with 95% ee in 92% yield. Treatment of **14** under Lewis-acid-assisted epoxy-ene cyclization completed the total synthesis of naturally occurring



Table 2 Optimization of Cu(I)-catalyzed oxidative N–N bond formation^{a,b}

S. no.	Condition	Solvent	Time	23a/23b	22
1	30 mol% Cu(I)L1	DCE	48 h	19% (~1 : 1)	62%
2	20 mol% Cu(I)Br:L1	DCE	48 h	42% (~1.1 : 1)	39%
3	20 mol% Cu(I)Br:L2	DCE	48 h	51% (~1.2 : 1)	31%
4	20 mol% Cu(I)Br:L3	DCE	48 h	23% (~1.1 : 1)	56%
5	20 mol% Cu(I)Br:L4	DCE	48 h	46% (~1.2 : 1)	32%
6	20 mol% Cu(I)Br 40 mol% DMAP	DCE	17 h	68% (~1.6 : 1)	—
7	20 mol% Cu(I)Br 40 mol% DMAP	MeCN	17 h	49% (1.6 : 1)	—

^a All the reactions were carried out in the presence of an O₂ balloon (1 atm). ^b Yields are reported as isolated yields after column chromatography.

R = H, L1
 R = *t*-Bu, L2
 L3
 L4

^a All the reactions were carried out in the presence of an O₂ balloon (1 atm). ^b Yields are reported as isolated yields after column chromatography.

4-*epi*-triptobenzene L (4) bearing a *trans*-decalin motif and four contiguous stereogenic centers in 63% yield (Scheme 3).¹⁶ The synthesized 4-*epi*-triptobenzene L (4) contained all the requisite stereogenic centers for the indolosesquiterpene alkaloids in place.¹⁷ Furthermore, a chemoselective oxidation of the 1,3-diol in the presence of PIDA and TEMPO followed by Pinnick oxidation and methylation with dimethyl sulfate (Me₂SO₄) furnished ester 9 in 76% yield (Scheme 3). Next, using the protocol described above, a mass of more than 10 g of compound 9 was prepared.

Next, aromatic electrophilic bromination of 9 with *N*-bromo succinimide (NBS) in acetonitrile afforded 8 in 92% yield

**Scheme 7** Total syntheses of dimeric indolosesquiterpene alkaloids 1a–b.**Scheme 8** A direct conversion of xiamycin A methyl ester (2b) into dimeric indolosesquiterpene alkaloids 1a–b.

(Scheme 4). Thus, the stage was set for the *ipso*-nitration,¹⁸ which was investigated under various conditions. Gratifyingly, the *ipso*-nitration of the isopropyl group of 8 was realized with fuming HNO₃ at –40 °C. Carrying out a nitration of the hydroxyl group afforded nitrite derivative 15 in 69% yield, with the identity of this derivative confirmed by X-ray analysis of its Suzuki–Miyaura coupling product (after recrystallization). Reduction of the nitro groups of 16 (10 mol% Pd–C under 1 atmosphere of H₂ gas) followed by the treatment with Ac₂O afforded acetanilide 6 in 92% yield over 2 steps (Scheme 4). At this point we were in a position to test the Buchwald¹⁹ oxidative C–N bond formation of acetanilide 6 to craft the pentacyclic core of xiamycin A (Scheme 4). Since molecular oxygen is a quintessential oxidizing agent that performs several dehydrogenative processes in the presence of substoichiometric amounts of high-valence transition-metal complexes and has important implications for the large-scale preparation of

pharmaceuticals and fine chemicals, we shifted our attention to a transition-metal-free process under an oxygen atmosphere.

Our initial attempt using a combination of 10 mol% Pd(OAc)₂ and 10 mol% Cu(OAc)₂ in toluene at 110 °C under an oxygen atmosphere was disappointing as acetanilide **6** provided a multitude of spots on the corresponding TLC with no expected product. We did isolate a 32% yield of pentacyclic ketone **18** and 19% yield of enone **19** along with 31% yield of the starting material acetanilide **6** (Scheme 4). Thus, a quick optimization using different solvents, oxidants and Pd(II) source was carried out; it revealed that DMSO was a good choice, where complete consumption of starting acetanilide **6** was observed. Interestingly, we observed a three-fold oxidative process of **6** in the presence of 10 mol% Pd(OAc)₂ in dimethylsulfoxide (DMSO) under an oxygen atmosphere (1 atm), without the use of a transition-metal based oxidant,²⁰ to afford an 83% isolated yield of enone **19** (Scheme 4).^{19,21} The same efficiency was observed when the oxidative reaction was carried out using 10 mol% Pd(TFA)₂ under an O₂ atmosphere (1 atm) in DMSO (85% yield of isolated enone **19**). In the presence of Pd and O₂, the secondary alcohol of **17** was proposed to have oxidized to ketone **18** (Scheme 5). Next, in a one-pot reaction, ketone **18** oxidized to corresponding α,β -unsaturated enone **19**. Here, the reaction may have proceeded *via* a C- and/or O-bound Pd-enolate (see, **17a–c** in Scheme 5). A β -hydride elimination was thought to have occurred *via* C-bound enolate to result in enone **19** (Scheme 5).

Since the secondary alcohol was responsible for the over-oxidation under Pd(II)-catalysis, it was protected with an acetate group. Hence, compound **16**, having an aromatic nitro group as well as a nitrite functionality, was reduced under hydrogenation conditions followed by a reaction with acetic anhydride to afford a 97% yield of acetanilide **20** (Scheme 6). Gratifyingly, 2-phenyl acetanilide **20** in the presence of 10 mol% Pd(OAc)₂ in dimethylsulfoxide (DMSO) under an oxygen atmosphere afforded *N,O*-bis-acetylated pentacyclic core **21** in 87% isolated yield, without the use of a transition-metal-based oxidant (Scheme 6).²⁰

Next, deacetylation of compound **21** upon treatment with K₂CO₃ in MeOH completed the synthesis of xiamycin A methyl ester (**2b**) in 96% yield. Furthermore, saponification of **2b** using a mixture of KOH and LiOH in a MeOH/H₂O mixture at reflux completed the synthesis of xiamycin A (**2a**), thus setting the stage for the dimerization *via* the key dehydrogenative N–N-bond-forming reaction.²²

To investigate the chemical feasibility of the biosynthetic hypothesis, we next pursued the key dehydrogenative N–N-bond-forming dimerization of xiamycin A (**2a**) and xiamycin A methylester (**2b**) using various oxidants such as I₂,^{6a} KMnO₄,^{6b} Ag₂O,^{6c} dichromate,^{6d} PIDA, KI or atmospheric O₂. Each of these conditions, however, simply led to decomposition or no conversion. Interestingly, while using I₂ and ⁿBuLi at –78 °C to 25 °C for 72 h,²³ xiamycin A methylester (**2b**) afforded 14% yields of dixiamycin A and B methyl esters (**24a** and **24b**) (dr *ca.* 1 : 1), 37% yield of recovered starting material along with multiple TLC spots, probably arising from oxidative C–N and C–C bond formations (Table 1). This result was indeed encouraging, and thus a variety of other oxidative conditions were tested to effect

a chemoselective N–N bond formation for dixiamycins A (**1a**) and B (**1b**).

After testing various conditions for this goal of chemoselective N–N bond formation, we turned our attention to aerobic oxidation employing Cu(I)-catalysis as reported by Stahl and coworkers.⁸ In this regard, our attempt at using natural product xiamycin A (**2a**) under the Stahl conditions (20 mol% Cu(I) Br·Me₂S and 40 mol% DMAP in dichloroethane at reflux for 17 h)⁸ led to decomposition. We found compound **2a** to be a challenging substrate due to its several functional groups. To meet this challenge, we decided to use xiamycin A methyl ester TMS ether (**22**) as a starting material where the carboxylic acid and secondary alcohol of xiamycin A **2a** were each in a protected form. Using the Cu(I)-catalyzed oxidative coupling conditions for **22** afforded promising N–N dimeric compounds **23a** and **23b**.

A detailed optimization of the Cu(I)-catalyzed aerobic oxidation of **22** is shown in Table 2. Following optimization, we found that treatment of **22** with 20 mol% Cu(I)Br and 40 mol% DMAP in DCE at reflux gave a 68% yield (*ca.* ~1.6 : 1 mixture) of the TMS ethers of dixiamycins A methyl ester (**23a**) and B methyl ester (**23b**) (entry 6). Other bidentate ligands (**L1–L4**) were found to be inferior to the DMAP ligand, affording the products in only 23–51% yields along with decomposition side products (entries 2–5). Note that the TMS protecting group in **22** survived under the reaction condition at 70 °C. These N–N atropo-diastereomers were found to be separable using column chromatography. Following treatment with K₂CO₃ in MeOH, the atropo-diastereomers were smoothly converted to the corresponding methyl esters of dixiamycins A and B, *i.e.*, **24a–b** (Scheme 7). Furthermore, saponification of **24a–b** with KOH and LiOH in MeOH/H₂O at 80 °C for 12–16 h completed the total syntheses of dixiamycins A (**1a**) and B (**1b**) without an event (Scheme 7). The atropo-diastereomeric natures of dixiamycins A (**1a**) and B (**1b**) were confirmed using a detailed HPLC analysis and their retention times were found to differ [^tR of dixiamycin A (**1a**) = 8.8 min and ^tR of dixiamycin B (**1b**) = 9.8 min] (see ESI† for detailed HPLC analysis).

To demonstrate the versatility of our synthesis, TMS protection was used as an orthogonal protecting group. In a one-pot operation (Scheme 8), **2b** was treated with TMSOTf in DCE followed by application of our optimal N–N-bond-forming conditions and subsequent TMS deprotection using K₂CO₃ in MeOH; this procedure afforded a direct approach to dixiamycins A and B methyl esters in 66% yield in a *ca.* 1.6 : 1 ratio (Scheme 8). In addition, Cu(I)-catalyzed aerobic oxidation of xiamycin A methyl ester (**2b**) afforded atropo-diastereomers **24a–b** in 42% yield upon prolonged heating (72 h) along with 31% recovered **2b**, consistent with the hypothesis of nature's oxidative approach to the dixiamycins.

Conclusions

In conclusion, a total synthesis of N–N atropo-diastereomers of indolosesquiterpene alkaloids, namely dixiamycins A (**1a**) and B (**1b**), was developed. This synthesis involved a key Cu(I)-catalyzed aerobic oxidation of xiamycin A methyl ester (**2b**), culminating in the first total synthesis of dixiamycin A (**1a**) bearing



the rare N–N bond. The monomer of this approach, xiamycin A methyl ester (**2b**), was synthesized from a naturally occurring diterpenoid, namely 4-*epi*-triptobenzene L (**4**), following key Buchwald oxidative C–N-bond-forming reactions to craft the pentacyclic core of indolosesquiterpene alkaloid **2b**. Thus, this synthesis featured the demonstration of two key aerobic oxidations, namely Pd(II)-(oxidative C–N bond formation) and Cu(I)-catalyzed (oxidative N–N bond formation) processes for the syntheses of, respectively, monomeric and dimeric indolosesquiterpene alkaloids. Our study also confirmed the high stability of the dixiamycins A (**1a**) and B (**1b**) under elevated temperature and basic conditions, suggesting that N–N atropo-diastereomers of the xiamycins could represent viable starting points for potential use in pharmaceuticals and agrochemicals.

Data availability

Data supporting this article have been uploaded as ESI.†

Author contributions

A. B. conceived and supervised this project. R. N. investigated the key oxidative N–N bond-formation leading to dixiamycins A and B. R. N., S. N., and S. K. investigated the catalytic polyene cyclization and synthesized all the starting materials. S. N., M. M., V. R. G., and R. M. investigated the oxidative C–N bond-formation to craft the pentacyclic core of xiamycin A methyl ester. A. B. and R. N. wrote the original draft of the manuscript which was edited by all authors.

Conflicts of interest

There are no conflicts to declare.

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