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Asymmetric Total Syntheses of (+)-Cinereain and (–)-Janoxepin via a Fragment Coupling/Retro-Claisen Rearrangement Cascade

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Abstract: The total syntheses of (+)-cinereain and (–)-janoxepin, two fungal cyclotripeptides featuring a complex heterocyclic core and interesting phytotoxic and antimalarial activities, have been achieved in a convergent manner. A key step in this synthesis is a one pot cascade initiated by the cyclocondensation of two fragments—a hindered 2-vinylcyclopropane-1-acyl fluoride and an electron deficient cyclic amidine—to release a reactive spiro[2-vinylcyclopropane-1,5'-pyrimidine-4',6'-dione]. This intermediate underwent a spontaneous retro-Claisen rearrangement that was rationalized by DFT calculations. The cascade directly afforded a 2,5-dihydrooxepin-fused heterotricyclic product. In addition, the challenging oxepin ring was finally forged by the palladium-catalyzed β -hydride elimination of an allylic fluoride intermediate. Beyond the development of these original transformations, this work contributes to the first achievement of the asymmetric total syntheses of (+)-cinereain and (–)-janoxepin.

Introduction

After the first isolation of the phytotoxin (+)-cinereain (**1**) in 1988 from *Botrytis cinerea* (Figure 1A),^[1] the noble rot that grows on decaying wine grapes, nearly forty parent compounds have been reported from other fungal sources until now.^[2] Among them, (–)-janoxepin (**2**) was isolated from *Aspergillus janus* in 2005 and showed interesting antimalarial properties.^[3] These fungal cyclotripeptides are based on the oxepin-pyrimidinone-ketopiperazine fused model and are intriguing from many points of view. Firstly, the rare oxepin motif (**3**) is a boat-shaped, non-aromatic, seven-membered oxacycle present in several natural products.^[4] Its valence tautomerism with benzene oxide (**4**), recently correlated to a heavy-atom quantum tunneling,^[5] was defined by Vogel in 1967 and involves a disrotatory 6 π -electrocyclization (Figure 1B).^[6] Secondly, compounds **1** and **2** are in fact biogenetically derived from

anthranilic acid and two amino acids, revealing their peptidic nature. Thirdly, the oxepin ring results from the late-stage oxidation of the anthranilic aromatic ring by a cytochrome P₄₅₀ monooxygenase via an arene oxide intermediate,^[7] as it occurs during the metabolism of benzene and other arenes.^[8,9]

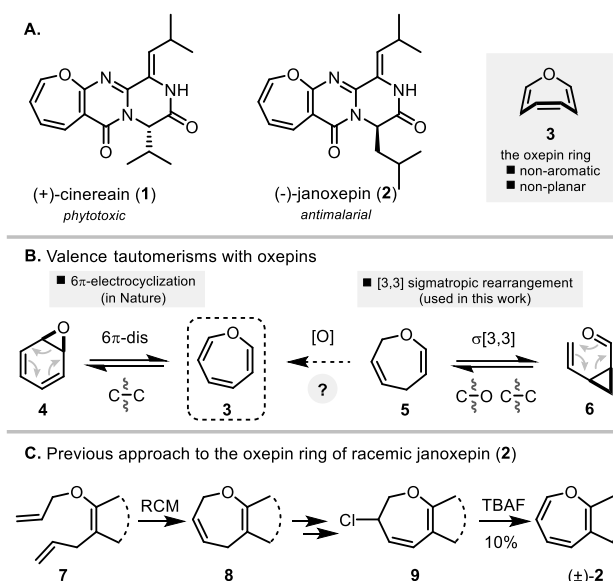


Figure 1. Structure of (+)-cinereain (**1**) and (-)-janoxepin (**2**) containing an oxepin ring (A). Valence tautomerisms with oxepins (B). Approach of Taylor and Doveston for the oxepin ring (C).^[10,11]

The structural and electronic properties of oxepins, and their occurrence in a significant set of stable biologically active compounds like **1** and **2** constitute appealing challenges for total synthesis.^[4,12] However only a handful of oxepin total syntheses have been reported so far,^[4] including that of a racemic version of janoxepin **2** by Taylor, Doveston and co-workers in 2012 (Figure 1C), which is also the unique synthetic report in this compound series.^[10,11] Additional synthetic efforts are therefore much needed to improve the availability of these compounds in order to study the potential agricultural and medicinal applications suggested by their biological properties.

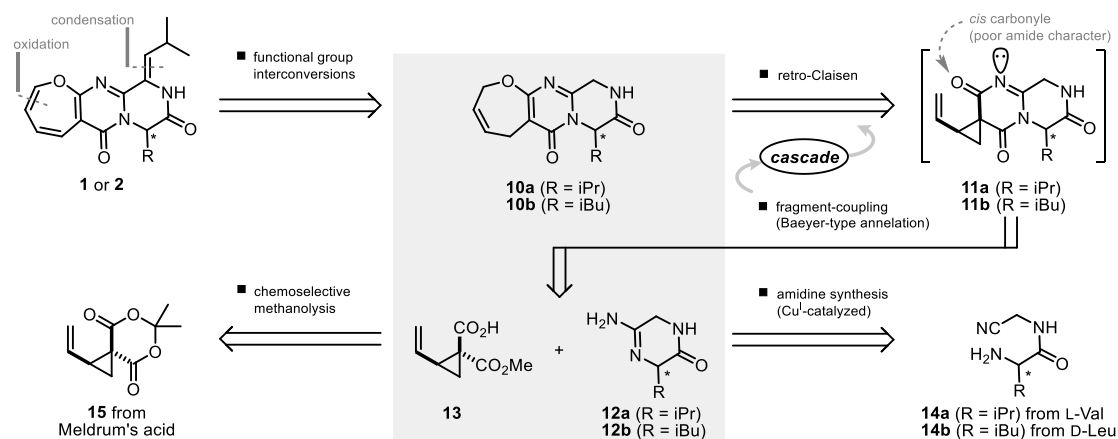
While there is no straightforward method to install directly an unsaturated oxepin ring on a complex synthetic target, the desaturation of dihydrooxepins (**5**) could be a powerful entry to the oxepin core (**3**), complementing other strategies including elimination reactions to generate reactive arene oxide precursors (**4**),^[13–15] ring enlargements,^[16–18] or a recent three-step sequence to convert arenes into oxepins.^[19] 2,5-Dihydrooxepin intermediates (**5**) can be obtained by the retro-Claisen [3,3]-sigmatropic rearrangement of 2-vinylcyclopropyl-1-carboxaldehydes (**6**), which is another valence tautomerism hypothesized by Vogel in 1963^[20] and experimentally confirmed by Rhoads and Cockroft in 1969 (Figure 1B).^[21] Further studies by Reissig^[22] and Boeckman^[23] showed the crucial influence of substituents on this equilibrium. In a recent report we demonstrated that this spontaneous rearrangement could be applied it to the total synthesis of radulanin A, a 2,5-dihydrobenzoxepin.^[24] Before our work, the retro-Claisen rearrangement had never been considered as a key-step in a total synthesis,^[25] probably due to the reputed kinetic instability of 2,5-dihydrooxepins (**6**).^[24,26,27] Furthermore, the oxidation to an oxepin from a 2,5-dihydrooxepin (**8**), prepared by ring-closing olefin metathesis of a diene (**7**), has only been investigated by Taylor and co-workers during the synthesis of (\pm)-**2** (Figure 1C).^[10,11] After extensive optimization attempts, only a 3-chloro-2,3-dihydrooxepin intermediate (**9**) underwent elimination in presence of a fluoride base, yet in a poor 10% yield. This low-yielding elimination step has left room for

further developments. Taking advantage of a highly convergent strategy enabled by the retro-Claisen rearrangement to construct the heterotricyclic core of these natural products, we now describe the first asymmetric total syntheses of (+)-**1** and (–)-**2**. On this occasion, the challenging oxepin ring has been successfully installed through a palladium-promoted β -hydride elimination of an allylic fluoride.

Results and Discussion

From the retrosynthetic point of view, the kinetic control and spontaneity of the retro-Claisen rearrangement of 2-vinylcyclopropyl-1-carbonyl intermediates led us to envisage a tandem fragment coupling strategy to construct tricyclic precursor **10** (**a**: R = iPr, **b**: R = iBu), which would be submitted to functional group manipulations towards the oxepin natural products **1** and **2** (Scheme 1). Fragments **12** and **13** could in principle be engaged in a cyclocondensation reaction to give 4,6-pyrimidinedione **11**, which would readily cyclize into **10**. We previously demonstrated that lactam carbonyls, unlike cyclic ketones, are not reactive towards the retro-Claisen rearrangement to form the 2,5-dihydrooxepin ring.^[24] In this case, however, **11** might favorably evolve toward **10** since the *cis*-carbonyl group involved in the rearrangement has a poor amide character due to the non-conjugation with the vicinal nitrogen lone pair. Amidine fragments **12** could result from an intramolecular cyclization of δ -aminonitriles **14** (made from the corresponding amino acid) involving the direct addition of the amine onto the nitrile group. Finally, the diastereoselective synthesis of cyclopropanecarboxylic acid **13** could be possible through the methanolysis of Meldrum's acid derivative **15**, which was supposed to occur on the less hindered oxycarbonyl, *trans* to the vinyl group on the cyclopropane.

The feasibility of the retro-Claisen rearrangement is shown by DFT calculations on model substrate **A** at the IEFPCM(DMF)-M06/6-311++G(2d,2p)//M06/6-311G(d,p) computational level including solvent (DMF) effects (Figure 2; see additional discussion in the Supporting Information and Figure S6). This rearrangement leading to 2,5-dihydrooxepine **B** is kinetically favored, with an activation barrier of +20.8 kcal mol⁻¹ ($\Delta G_r = -1.8$ kcal mol⁻¹) through transition state **TS1**. Theoretically, it might be competing with the Cope-Wilson [1,3]-sigmatropic rearrangement through **TS2**, leading to the thermodynamic five-membered product **C**, with nevertheless a noticeably higher activation barrier of +27.1 kcal mol⁻¹ ($\Delta G_r = -5.7$ kcal mol⁻¹). We will see later that, in agreement with these calculations, this second rearrangement was not observed in this study. Furthermore, for comparison purpose, we calculated a similar rearrangement involving the amide carbonyl group, leading to products with less thermodynamic stability than the reactant (see Figure S6 in the SI: from **D** to **E** and **F**).



Scheme 1. Retrosynthetic analysis of (+)-cinereain (**1**, R = iPr) and (-)-janoxepin (**2**, R = iBu).

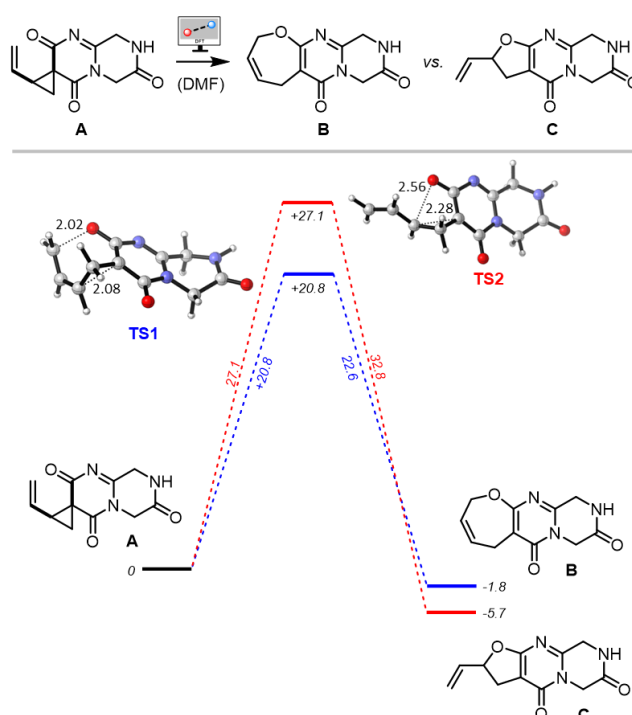
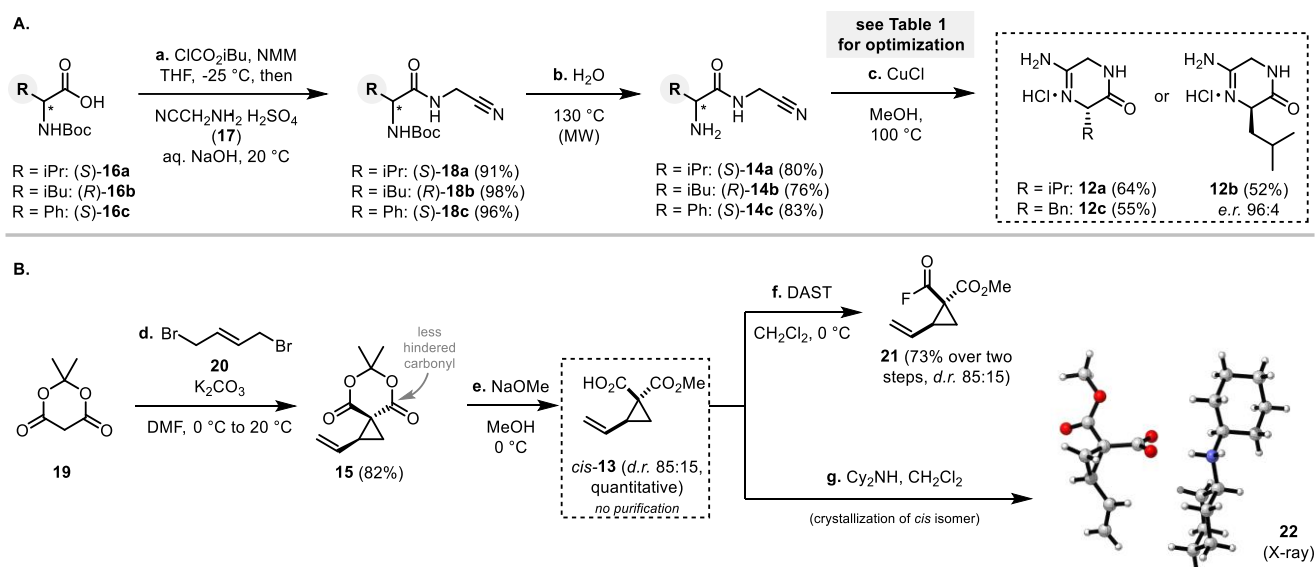


Figure 2. Energy profile of the retro-Claisen and Clowe-Wilson rearrangements of simplified (no substituent) model **A** (full reaction path including all conformers in Figure S6). Gibbs free energies relative to starting materials are given in kcal mol⁻¹.

To synthesize amidine fragments **12a** and **12b** (Scheme 2A), *N*-Boc-protected l-valine (**16a**) and d-leucine (**16b**) were first activated as mixed anhydrides using ClCO₂iBu and engaged in peptide coupling with aminoacetonitrile (**17**), affording the corresponding amides **18a** and **18b** in excellent yields.^[10] Subsequent deprotection into **14a** and **14b** under microwave heating in water^[28] led to better outcomes than the HCO₂H-mediated Boc-cleavage. A two-step cyclization of amide-tethered δ -aminonitriles into amidines had previously been reported by Isobe and co-workers^[29] and later applied by Taylor in the synthesis of janoxepin.^[10] This cyclization involved an oximation in the presence of hydroxylamine, followed by an hydrogenation with Raney nickel. Reproducibility issues with this method forced us to investigate an alternative one-step methodology for the synthesis of cyclic amidines **12a** and **12b** from δ -aminonitriles **14a** (here used for optimization of the conditions) and **14b**, through an acid-catalyzed

cyclization. Among Brønsted acids, only acetic acid afforded at 140 °C the expected product **12a** from **14a**, yet in a moderate 46% yield that could not be further improved. Concerning Lewis acids, while TMSOTf, AlCl₃, Sc(OTf)₃ or FeCl₃ did not promote the reaction, CuCl in MeOH at 100 °C gave 64% of amidine **12a** (Table 1, entry 1), which notably appeared to be highly hygroscopic. Interestingly, the use of CuCl₂ resulted in similar yields (entry 2), but Cu(OTf)₂ was inefficient (entry 3). Although the details of the interchangeability of CuCl and CuCl₂ in this reaction were not investigated, the complex redox behavior of these salts in alcohol solutions with a key role of chloride counter-ions has already been reported in the literature.^[30] The use of methanol was crucial for the success of this reaction since a replacement by ethanol only resulted in traces of product **12a** (entry 4). Incidentally, even though Cu(MeCN)₄PF₆ allowed the cyclization of **14a** in good 74% yields at 60 °C, supporting the role of Cu(I) species in this reaction (entry 5), practical and cost reasons discouraged us from applying this condition on a larger synthetic scale. Using optimized conditions (see entry 1), analogous amidine **12b** was also synthesized in 52% yield. By comparison with a racemic sample obtained from dl-leucine by the same synthetic route, the chiral HPLC analysis of **12b** (Chiralpak® IC-3 column) showed that most of the enantiomeric integrity of the sample was conserved (Figure S1), with an enantiomeric ratio of 96:4 (similar analyses were unsuccessful on **12a**, in spite of three columns tested).



Scheme 2. Synthesis of fragments **12** (A) and **13** (B). *Reagents and conditions:* (a) ClCO₂iBu (1.1 equiv), NMM (1.1 equiv), THF, −25 °C, 15 min; then **17** (1.1 equiv), aq. NaOH (1.4 equiv, 1 M), 0 °C to 20 °C, 18 h; (b) H₂O, 130 °C (microwave), 50 min; (c) CuCl (0.5 equiv), MeOH, 100 °C, 2 h; (d) K₂CO₃ (1.5 equiv), DMF, 0 °C, 10 min; then *trans*-1,4-dibromo-2-butene (**20**, 1.5 equiv), 0 °C to 20 °C, 2 h; (e) Na (1.2 equiv), MeOH, 0 °C, 30 min (**13** is unstable and should be used directly); (f) DAST (0.7 equiv), CH₂Cl₂, 0 °C, 30 min, 73% over two steps; (g) **13** (1 equiv), Cy₂NH (1 equiv), CH₂Cl₂ (X-ray structure: CCDC 2178745).

Both amidines **12a** and **12b** could finally be prepared in multigram scales through this method. Finally, an l-phenylalanine derivative afforded amidine **12c** in 55% yield. Although this compound is not related to the total synthesis of **1** and **2**, its synthesis unexpectedly revealed the hydrochloride nature of the amidine function, after X-ray crystallography (Figure S5; CCDC 2189422), suggesting that amidines **12a** and **12b** are HCl salts.

Table 1. Condition screening for the copper-catalyzed conversion of **14a** into amidine **12a** (Scheme 2, step c).

entry	catalyst (equiv)	solvent (°C) ^[a]	yield (%)
1	CuCl (0.5)	MeOH (100)	64 ^[b]
2	CuCl ₂ (0.5)	MeOH (100)	62 ^[b]
3	Cu(OTf) ₂ (0.5)	MeOH (100)	– ^[c]
4	CuCl (0.5)	EtOH (100)	trace
5	Cu(MeCN) ₄ PF ₆ (0.5)	MeOH (60)	74

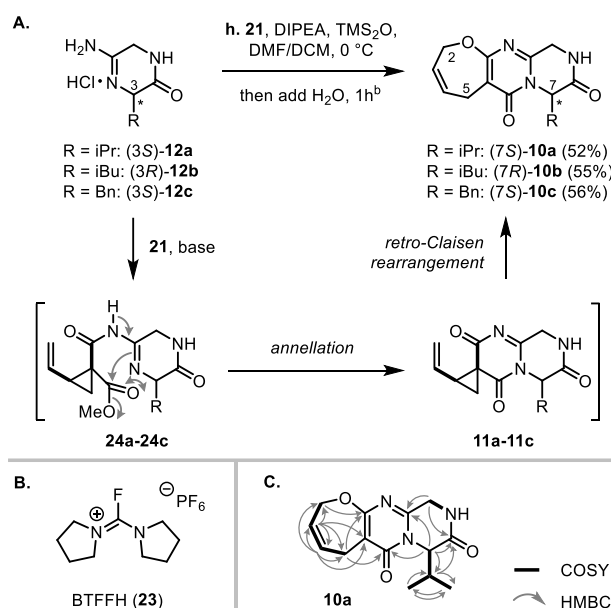
[a] Sealed tube during 2 hours (the optimal conditions of entry 1 could be performed under strong reflux without affecting yields). [b] HCl salt (see text). [c] No reaction.

Concerning fragment **13**, the reaction of Meldrum's acid (**19**) with 1,4-dibromobutene (**20**) in DMF in the presence of K₂CO₃ afforded vinylcyclopropane derivative **15** in 82% yield (Scheme 2B). Chemoselective methanolysis of the less hindered carboxylate, at 0 °C with sodium methoxide, resulted in the *cis*-vinylcyclopropane carboxylic acid (*cis*-**13**) with a diastereoselectivity of 85:15. The structure of *cis*-**13** was confirmed by X-ray crystallography of dicyclohexylammonium carboxylate **22** (CCDC 2178745).

With amidines **12a-12b** and acid **13** in hand, a peptide coupling was investigated, foreseeing the possibility of a tandem 4,6-pyrimidinedione cyclocondensation and retro-Claisen rearrangement to form the tricyclic dihydrooxepin scaffolds **10a** and **10b** (Scheme 3A). The screening of activating reagents like ClCO₂iBu, EDCI, HATU, HBTU, BOP, EEDQ, T3P or FDPP (see Figure S3) in the presence of DIPEA in DMF led to complex mixtures of products. While peptide coupling issues are generally thought to be resolved, only few methods are available to address the coupling of electron deficient amines (like amidines **12**) with hindered carboxylic acids (like **13**). Based on the literature,^[31] such a coupling can be improved by the use of fluorouronium reagents such as bis(tetramethylene)fluoroformamidinium hexafluorophosphate (BTFFH, **23** in Scheme 3B).^[32] In the presence of BTFFH and DIPEA in DMF at 20 °C, the desired 2,5-dihydrooxepin scaffold **10a** (confirmed by NMR experiments, see Scheme 3C) was indeed isolated in 10 to 27% yields, not only showing the feasibility of this amide coupling, but also fulfilling the promising application of the tandem retro-Claisen rearrangement to our synthesis. The efficiency of this transformation turned out, though, to be highly variable.

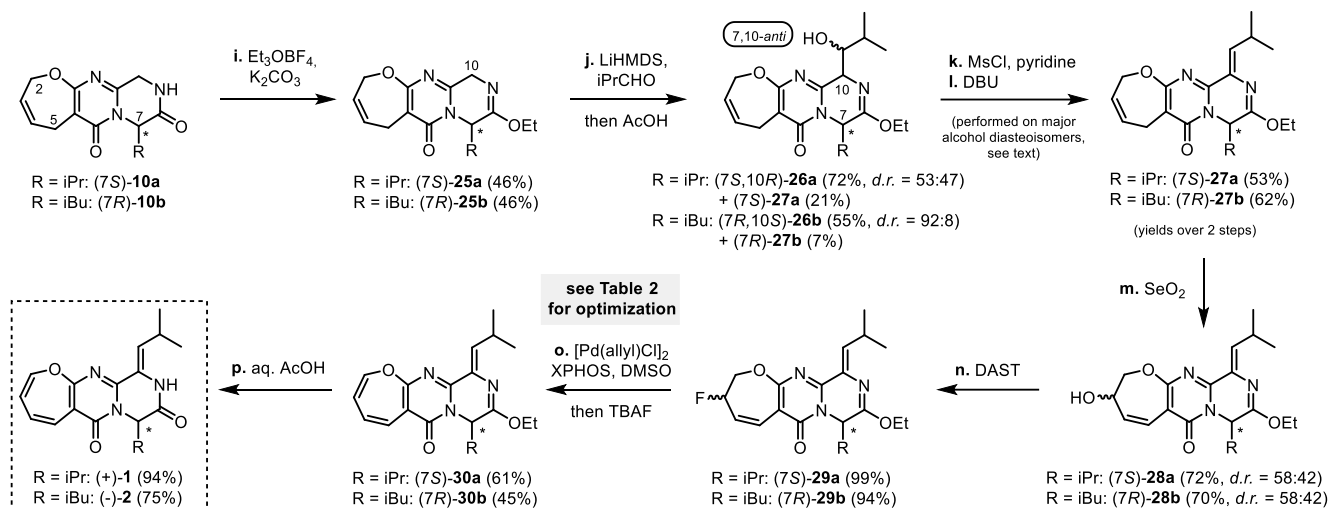
Noteworthy, since BTFFH differs from the majority of coupling reagents by involving an acyl fluoride intermediate (**21**) with the lowest steric hindrance,^[32] we decided to synthesize **21** by fluorination of carboxylic acid **13** in the presence of DAST (Scheme 2B) and engage it in the coupling step with **12a**. After a meticulous optimization of the conditions, the slow addition of acyl fluoride **21** onto amidine **12a** at 0 °C, in the presence of DIPEA and TMS₂O as a fluoride scavenger^[33] in DCM:DMF (3:1), afforded **10a** in 52% yield. Note that a long water treatment at room temperature was optimal at the end of the reaction, supposedly improving the last cyclocondensation step through **24a** toward the 4,6-pyrimidinedione ring (**11a**) before the retro-Claisen rearrangement occurs. Gratifyingly under these conditions, tricyclic products **10b** and **10c** were also obtained in 55% and 56% yields (Scheme 3). In spite

of seemingly moderate yields, these products result from a one-pot transformation involving the formation of two C–N bonds and a retro-Claisen rearrangement (*i.e.*, 80–82% yield per bond formed for **10a–10c**). Furthermore, the Cloke-Wilson isomer (**C** in Figure 2) was not observed.



Scheme 3. Synthesis of tricyclic scaffolds **10a–10c**, and mechanism of their formation (A). Structure of BTFFH (**23**) (B). NMR correlations on **10a** (C). *Reagents and conditions:* (h) Optimized conditions: DIPEA (4.5 equiv), TMS₂O (2.0 equiv), CH₂Cl₂/DMF (3:1), 0 °C, 10 min; then slow addition of **21** (1.5 equiv) in CH₂Cl₂, 0 °C; then H₂O, r.t., 1 h. *Note:* Polar decomposition products were observed. 15% of the reaction mixture should contain end-products resulting from the *trans* acyl fluoride isomer of **21** (*d.r.* 85:15).

Tricyclic intermediates **10a** and **10b** were then protected as ethyl imidates **25a** and **25b** in the presence of Et₃OBf₄ and K₂CO₃ (Scheme 4). After deprotonation of position C-10 by LiHMDS, an aldol reaction with isobutyraldehyde afforded alcohols **26a** and **26b** in 72% and 55% yields as mixtures of separable diastereoisomers. In both cases, the elimination products **27a** and **27b** were also obtained in 21% and 7% yields. We relied on Schöllkopf's studies on the asymmetric aldol addition of lithiated bislactim ethers to predict the stereoselectivity,^[34,35] revealing the major *syn* (*threo*) diastereoisomers (7*S*,10*R*,11*S*)-**26a** and (7*R*,10*S*,11*R*)-**26b** (Figure 4). Surprisingly, the stereoselectivity was repeatedly very different for the two substrates (53:47 for **26a** and 92:8 for **26b**). Through an E2 mechanism, these diastereoisomers will afford the correct *Z*-geometry during the next elimination step.



Scheme 4. Synthesis of (+)-cinereain (**1**) and (–)-janoxepin (**2**). *Reagents and conditions:* (i) MS 4Å, K₂CO₃ (4.0 equiv), CH₂Cl₂, 0 °C; then Et₃OBF₄ (1.5 equiv, slow addition over six hours), CH₂Cl₂, 0 °C, 13 h; (j) LiHMDS (2.1 equiv), THF, –78 °C; then **25a** or **25b** (1 equiv), –78 °C, 10 min; then iPrCHO (3 equiv), –78 °C, 10 min; then AcOH (0.60 mL/mmol), –78 °C to r.t., 30 min; (k) MsCl (2 equiv), pyridine, r.t., 13 h; then DBU (2 equiv), 50 °C, 1.5 h; (m) SeO₂ (1.5 equiv), 1,4-dioxane, 90 °C, 1 h; (n) DAST (1.0 equiv), CH₂Cl₂, 0 °C, 15 min; (o) [Pd(allyl)Cl]₂ (0.5 equiv), XPhos (2.2 equiv), DMSO, r.t., 30 min; then **29a** or **29b** (1.0 equiv), DMSO, r.t., 30 min; then TBAF (1.5 equiv), r.t., 1 h; (p) 80% aq. AcOH, 50 °C, 1–4 h.

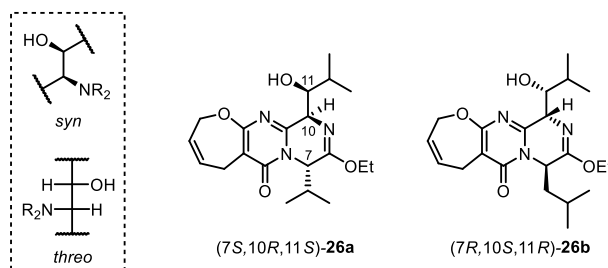
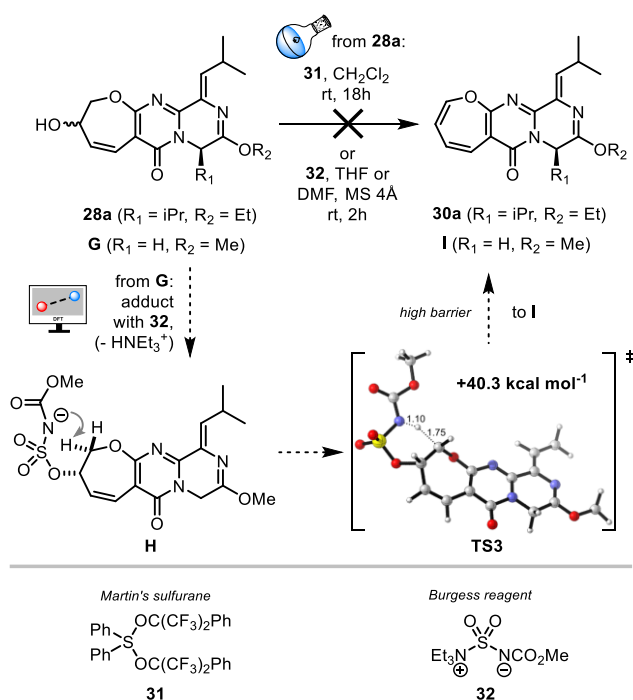


Figure 4. Predicted structures of the major *syn* (*threo*) aldol diastereomers **26a** and **26b**.^[34,35] The dotted frame shows the application of this nomenclature to (7S)-**26a**.

Thus, the isobutylidene substituent was installed by mesylation of the *syn* diastereoisomers followed by *anti*-elimination in presence of DBU, leading to *Z*-alkenes **27a** (53%) and **27b**^[10] (62%). Comparatively, a similar treatment of the diastereomeric alcohol (7S,10R,11R)-**26a** led to the same alkene **27a** in a lower yield of 30%, supposedly through an E1cB mechanism.

Several strategies were finally considered to install the oxepin ring by the oxidation of the 2,5-dihydrooxepin. This late step turned out to be, euphemistically, extremely challenging. Unsuccessful oxidation-elimination sequences were initially applied to the retro-Claisen product **10a** or on the functionalized intermediate **27a** (dihydroxylation/mesylation/TBAF treatment,^[24] bromination or Schenck-ene reactions,^[36] DDQ-mediated dehydrogenation^[37]), only resulting in the degradation of these sensible substrates. Similar difficulties had previously been encountered by Taylor and Doveston.^[10,11] However, the allylic oxidation of **27a** and **27b** in the presence of SeO₂ chemoselectively afforded allylic alcohols **28a** and **28b** in 70–72% yields (*d.r.* 60:40), leading us to dedicate all our efforts to achieving the elimination of this alcohol to form the oxepin ring. First, operating on **28a**, the

elimination by using Martin's sulfurane (**31**)^[38] or the Burgess reagent (**32**)^[39] failed to afford the desired oxepin product **30a**. This difficulty to eliminate the hydroxyl group may be the result of subtle conformational effects in this 2,3-dihydrooxepin ring system, fixing the activated alcohol in an equatorial position or leading to poor orbital overlap, precluding any E1 or E2 mechanism. In the case of the Burgess reagent, DFT calculations on theoretical anionic adduct **H** confirmed the high activation barrier to reach transition state **TS3** (+40.3 kcal mol⁻¹) leading to product **I**, impeding the *syn*-elimination (Scheme 5; see also Figure S7 and additional discussion in the supporting information).



Scheme 5. Elimination attempts to generate the oxepin ring from **28a** under Martin's or Burgess' conditions, and DFT calculation on model adduct **H** (from **G**), showing a high activation barrier through **TS3** to get **I**.

Table 2. Optimization of the elimination step for the oxepin synthesis from substrate **29a**

entry	catalyst (equiv)	ligand (equiv)	base (equiv)	solvent	yield (%)
1	-	-	TBAF (1.5)	DMSO	CM ^[a]
2	[Pd(allyl)Cl] ₂ (0.5)	XPhos (2.2)	-	DMSO	N.R. ^[b]
3	[Pd(allyl)Cl] ₂ (0.5)	XPhos (2.2)	TBAF (1.5)	DMSO	61 ^[c]
4	[Pd(allyl)Cl] ₂ (0.5)	XPhos (2.2)	TBAF (1.5)	CH ₂ Cl ₂	32 ^[c]
5	[Pd(allyl)Cl] ₂ (0.05)	XPhos (0.22)	TBAF (1.5)	DMSO	20 ^[d]
6	[Pd(allyl)Cl] ₂ (0.1)	XPhos (0.44)	TBAF (1.5)	DMSO	30 ^[d]
7	Pd(PPh ₃) ₄ (0.1)	-	TBAF (1.5)	CH ₂ Cl ₂	N.R. ^[b]
8	[Pd(allyl)Cl] ₂ (0.1)	XPhos (0.44)	DIPEA (2.0)	DMSO	N.R. ^[b]

[a] CM = complex mixture. [b] No reaction. [c] Isolated yield. [d] Conversion measured by ^1H NMR.

During these efforts, we noticed that the treatment of alcohols **28a** and **28b** with DAST at 0 °C proceeded in excellent fluorination yields (>94%), providing allyl fluoride intermediates **29a** and **29b** (Scheme 4). An analogous chlorinated derivative had previously been described to furnish low elimination yields by using TBAF (see Figure 1C).^[10] With our fluorinated intermediate, neither TBAF nor a stronger base like DIPEA promoted the fluoride elimination (Table 2, entry 1), in accordance with the known slow rates of HF elimination compared to HCl (*ca.* five orders of magnitude).^[40] Nevertheless, according to Gouverneur and co-workers, allyl fluorides are good substrates in palladium-catalyzed allylic substitutions, while undesired β -hydride eliminations can occasionally be observed when tBuXPhos is used as a ligand in presence of $[\text{Pd}(\text{allyl})\text{Cl}]_2$.^[41,42] We took advantage of this observation to induce the elimination of the fluorine substituent on **29a** and **29b**. While the couple of $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (50 mol%)/XPhos (2.2 equiv) was unreactive toward our substrates (entry 2), the consecutive addition of TBAF (1.5 equiv) to the reaction gratifyingly led to the rapid β -hydride elimination at room temperature, and furnished oxepin product **30a** in 61% yield (entry 3). Although the fluoride anion released after palladium addition was expected to serve as a potential base during this reaction, the addition of an excess amount of TBAF was essential to the success of this reaction. It also suggests a possible sequestration of the released fluoride through coordination to the metal. Furthermore, trying to change the solvent (CH_2Cl_2 , entry 4), or to lower the catalyst loading (entries 5 and 6), only resulted in lower yields. Replacing $[\text{Pd}(\text{allyl})\text{Cl}]_2$ by $\text{Pd}(\text{PPh}_3)_4$ (entry 7), or TBAF by DIPEA (entry 8), was unproductive. Finally, applying the best conditions (entry 3) to substrate **29b** led to protected janoxepin precursor **30b** in 45% yields.

The deprotection of the ethyl imidate group was then performed in aqueous acetic acid to afford (+)-cinereain **1** and (–)-janoxepin **2** in 94% and 75% yields. Chiral HPLC analyses of these synthetic natural products, based on Taylor's conditions for racemic janoxepin,^[10] indicated enantiomeric ratios of 87:13 and 90:10 for **1** and **2**, respectively, showing only little epimerization issues during the overall synthetic route. These products were also identical to the fungal natural products reported in the literature (Table S1 and S2).^[1,3] It must be noted that the specific optical rotation of (+)-cinereain ($[\alpha]_{\text{D}}^{25} = +71.9^\circ$, *c* 0.55, CHCl_3) was not previously reported, while that of (–)-janoxepin ($[\alpha]_{\text{D}}^{25} = -34.7^\circ$, *c* 0.19, MeOH) shows a 10-fold discrepancy compared to the reported natural product ($[\alpha]_{\text{D}}^{25} = -3.4^\circ$, *c* 1.49, MeOH).^[3] Considering that Taylor's racemic synthesis of janoxepin does not allow any comparison, this difference implies two possible explanations. Firstly, the isolated natural product could be in a quasi-racemic form. This hypothesis is highly speculative, though, due to the amino acid biosynthetic origin of janoxepin. Secondly, a wrong value could have been reported for the isolated natural product (unfortunately, it was not possible to reach the authors of this isolation work for discussion). However, comparison of the optical rotation of (–)-janoxepin with analogous natural products sharing the isobutyl substituent, *i.e.* (+)-oxepinamides L ($[\alpha]_{\text{D}}^{25} = +35.2$, *c* 0.071, MeOH) and M ($[\alpha]_{\text{D}}^{25} = +25.9$, *c* 0.027, MeOH),^[43] supports this second hypothesis.

Conclusion

We have completed the first asymmetric total syntheses of (+)-cinereain (**1**) and (–)-janoxepin (**2**) in eleven linear steps from commercially available compounds. The key step of our strategy involved a tandem fragment-coupling/retro-Claisen rearrangement, allowing a straightforward access to the heterotricyclic core of the natural products. Interestingly, our synthetic works provide the first

application of the retro-Claisen rearrangement of 2-vinylcyclopropylcarbonyl intermediates to total synthesis, sixty years after Vogel's first hypothesis on its existence.^[20] Furthermore, several methodological studies were accomplished, including a Cu(I)-catalyzed synthesis of cyclic amidine fragments **12**, a stereoselective synthesis of the vinylcyclopropane fragment **13**—a donor-acceptor cyclopropane that could find other applications in organic synthesis—, and an oxepin formation through the Pd-catalyzed elimination of an allylic fluoride. Overall, this work provides a rapid strategy to the access of highly functionalized natural cyclotriptides, with the help of creative synthetic methodologies.

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