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Towards the Synthesis of Dihydrooxepino[4,3-*b*]pyrrole-Containing Natural Products via Cope Rearrangement of Vinyl Pyrrole Epoxides

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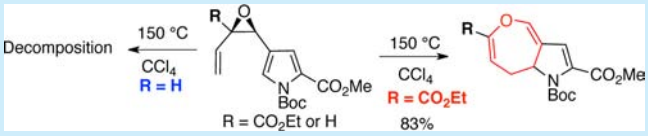
Supporting Information

ABSTRACT: An approach to the dihydrooxepino[4,3-*b*]-pyrrole core of diketopiperazine natural products which utilizes a vinyl pyrrole epoxide Cope rearrangement was investigated. It was found that an ester substituent on the epoxide was essential for the [3,3]-rearrangement to occur. Density functional calculations with M06-2X provided explanations for the effects of the pyrrole and ester groups on these rearrangements.



The dihydrooxepine-containing natural product aranotin (**1**)[1] was isolated in 1968 and is a member of a large family of thiodiketopiperazine natural products (Figure 1).[2,3] The related thiodiketopiperazine acetylaranotin (**2**)[4] was isolated from *Arachniotus aureus* and differs from **1** only by the extra acyl group. The structural features of compounds **1** and **2** are the dihydrooxepino[4,3-*b*]pyrrole and an epidithiodioxopiperazine ring system.

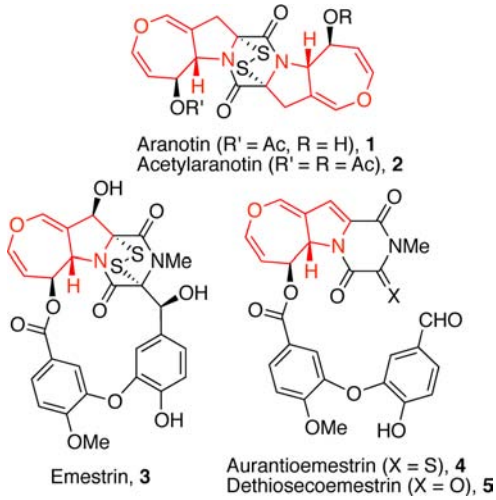
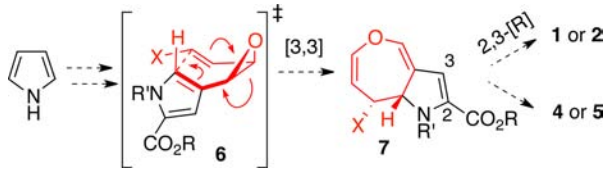


Figure 1. Dihydrooxepino[4,3-*b*]pyrrole-type natural products.

Emestrin (**3**) was isolated from the fungus *Cladorrhinum* in 1986, and its structure was confirmed by X-ray analysis (Figure 1).[5] Aurantioemestrin (**4**) was isolated from *Emericella striata* and appears to be a naturally occurring degradation product of **3**.[6] Compound **4** contains an ester derived from violaceic acid[7] and a dihydropyrrole, which probably arises from elimination of a hydroxyl group. Dethiosecoemestrin (**5**)[8] is the congener of **4** and has an oxamide functionality instead of a thioamide. Recently, the biosynthesis of acetylaranotin **2** has been elucidated using genome-based deletion analysis.[9] This work suggests that a benzene epoxide is involved in the cyclization to form the pyrrole, and further oxidative rearrangement gives the dihydrooxepino[4,3-*b*]pyrrole core.

Several approaches to the dihydrooxepino[4,3-*b*]pyrrole system of this family of natural products have been reported,[10−14] and two total syntheses of **2** have been achieved to date.[15,16] Inspired by the work of White,[17,18] we elected to investigate a divinyl epoxide-type rearrangement[19−21] of vinyl pyrrole epoxides[22] as a route to the fused oxepinepyrrole system of these natural products, starting from a simple pyrrole derivative. As shown in Scheme 1, elaboration of pyrrole to the vinyl epoxide **6** followed by Cope rearrangement would afford the core dihydrooxepine **7** of the dihydrooxepino[4,3-*b*]pyrroles **4** and **5** in a short sequence. In addition, selective conjugate reduction of the 2,3-alkene would provide access to the saturated derivatives, such as **2**.

Scheme 1. Vinyl Pyrrole Epoxide Cope Rearrangement Approach to Dihydrooxepino[4,3-*b*]pyrroles



The Cope rearrangement should be more facile for the (*E*)-alkene due to a boatlike transition state[17] and would afford the

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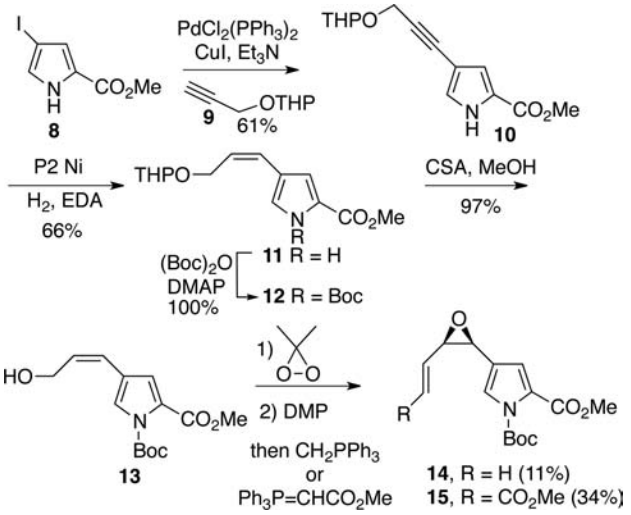
relative stereochemistry shown. Inversion at a later stage of the synthesis should introduce the correct configuration.

The synthesis of several model vinyl pyrrole epoxides is shown in Scheme 2. Iodide **8**, readily synthesized from commercially

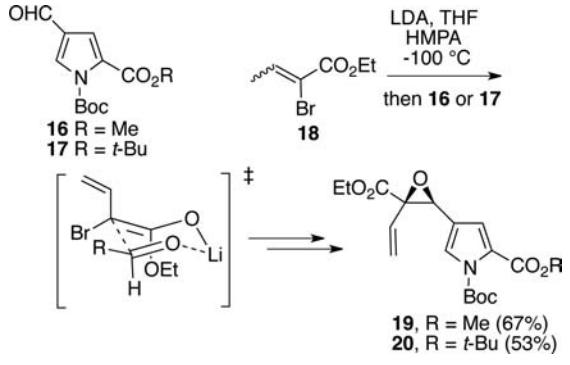
Scheme 2. Synthesis of Vinyl Epoxides 14 and 15



available 2-(trichloroacetyl)pyrrole,[23] underwent Sonogashira coupling[24] with the alkyne **9** to provide alkyne **10** in 61% yield. P2 Ni-mediated partial reduction[25] gave the alkene **11**, and the pyrrole nitrogen was protected with a Boc group to give carbamate **12**. Removal of the THP protecting group gave the allylic alcohol **13**, but epoxidation with reagents such as MCPBA did not afford the desired epoxide. Eventually, we found that treatment of alkene with an anhydrous solution of DMDO in acetone[26] afforded the labile epoxide in good yield. Oxidation with Dess–Martin periodinane followed by simple Wittig extension provided vinyl epoxide **14** in very low yield. The unsaturated ester **15** was synthesized in higher yield using a stabilized ylide.

An alternative and shorter approach to vinyl epoxides is shown in Scheme 3. This is based on a vinylogous Darzens reaction[22,27−29] and commences with the known pyrrole aldehyde **16**, again available from 2-(trichloroacetyl)pyrrole.[30] Treatment of bromocrotonate **18** with LDA at −100 °C followed by addition of the resultant enolate to the aldehyde **16** afforded the vinyl epoxide **19** as a single stereoisomer in good yield. This condensation presumably proceeds via the chairlike transition

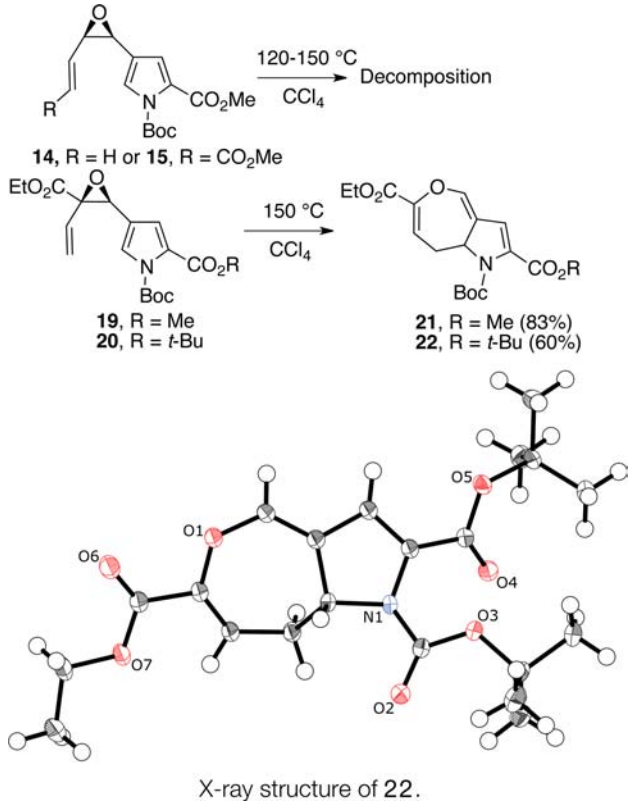
Scheme 3. Synthesis of Vinyl Epoxides via a Vinylogous Darzens Reaction



state[28] shown in Scheme 3 to result in the epoxide with the vinyl and pyrrole groups *cis* to each other. Addition of the anion derived from **18** to the aldehyde **17** also provided vinyl epoxide **20** as a single stereoisomer.

With several vinyl pyrrole epoxides in hand, we next investigated the Cope rearrangement (Scheme 4). Unfortu-

Scheme 4. Vinyl Pyrrole Epoxide Cope Rearrangement Studies



X-ray structure of **22**.

nately, attempted rearrangement of either **14** or **15** by heating in CCl_4[18] at 120–150 °C resulted in slow decomposition along with epoxide ring opening and no desired dihydrooxepine. On the other hand, heating a CCl_4 solution of vinyl epoxide **19** in a sealed tube at 150 °C resulted in smooth rearrangement to afford dihydrooxepino[4,3-*b*]pyrrole **21** in good yield. Similarly, heating vinyl epoxide **20** also afforded the dihydrooxepino[4,3-*b*]pyrrole **22**, the structure of which was confirmed by X-ray crystallography (Scheme 4).[31] Thus, it appears that the ester functionality on the epoxide is critical to the success of this [3,3]-rearrangement. It has been reported[20] that the Cope rearrangement of parent *cis*-2,3-divinylepoxide proceeds quantitatively at 98 °C in CCl_4. Therefore, the ester substituent is not essential for the rearrangement per se but appears to counteract a deactivating effect of the pyrrole.

We used DFT calculations[32] to understand the effects of the pyrrole and ester groups on the Cope rearrangement. A series of model divinyl epoxides **S1**–**S6** and the transition states for their Cope rearrangements (Figure 2) were computed at the M06-2X/6-311+G(d,p) level of theory,[33] simulating the solvent CCl_4 with the SMD[34] implicit model. In this series of divinyl epoxides, **S4** mimics the experimental substrate **14**, **S5** mimics **15**, and **S6** mimics **19** and **20** (modeling the Boc protecting group as CO_2Me).

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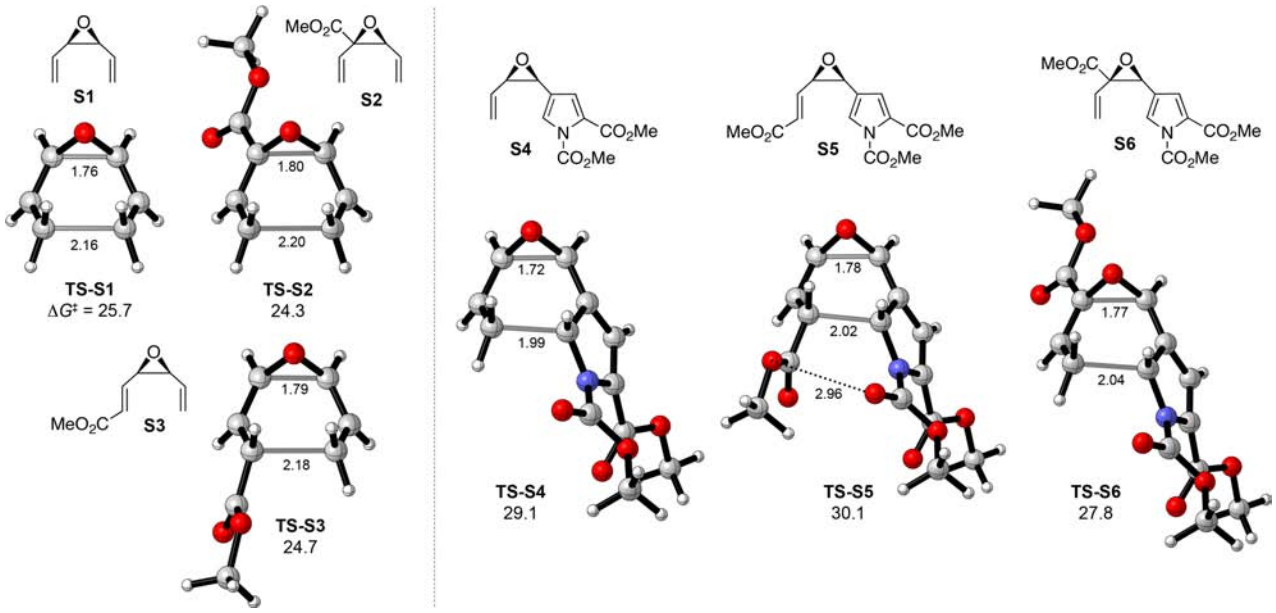

Figure 2. Transition states and activation energies of Cope rearrangements of divinyl epoxides **S1**−**S6** in CCl_4, computed with M06-2X/6-311+G(d,p)-SMD. Bond lengths in Å; $\Delta G^{\ddagger}$ in kcal/mol.

The Cope rearrangements of divinyl cyclopropane and several heteroatom-containing derivatives have previously been studied with B3LYP density functional calculations.[35,36] The preference for these dienes to rearrange via boat TSs rather than chair TSs is large. The M06-2X computations (Figure 2) predict that the Cope rearrangement of the parent divinyl epoxide **S1** has an activation energy $\Delta G^{\ddagger}$ of 25.7 kcal/mol (**TS-S1**). Compared to this, an ester substituent on the epoxide lowers the barrier by 1.4 kcal/mol (**TS-S2**). This is consistent with previous theoretical studies[37] which showed that in the Cope rearrangement of acyclic 1,5-hexadienes, the incorporation of a π-acceptor at C3 lowered the barrier for rearrangement. The substituted TS is stabilized by conjugation between the π-acceptor group and the developing double bond. On the other hand, incorporation of a π-acceptor at C1 of an acyclic 1,5-hexadiene has previously been shown to raise the barrier for Cope rearrangement.[38] In the corresponding divinyl epoxide **S3**, however, the opposite effect is observed, where the ester lowers the barrier by 1 kcal/mol. In **TS-S3**, stabilization arises because the resonance scheme contains an additional contributor in which the oxygen, double bond, and ester group form an extended conjugated π-system.[39]

Consistent with the failure of divinyl epoxide **14** to furnish rearranged product (Scheme 4), the barrier for rearrangement of vinyl pyrrole epoxide **S4** is computed to be 3.4 kcal/mol higher than that of divinyl epoxide itself (**TS-S4**, $\Delta G^{\ddagger}$ = 29.1 kcal/mol). The pyrrole group is a less reactive equivalent of a vinyl group, which undergoes dearomatization during the rearrangement. The TS occurs at a later stage along the reaction coordinate, with a 0.17 Å shorter forming C−C bond and more advanced pyramidalization of the carbon atoms within the two vinyl moieties. These structural distortions are estimated to be collectively worth approximately 5 kcal/mol (by dissecting **S1**/**S4** and **TS-S1**/**TS-S4** into vinyl and pyrrole fragments and computing the energies of the individual fragments separately). Incorporation of an ester substituent on the vinyl terminus produces a further 1 kcal/mol increase in the barrier (**TS-S5**). This mirrors the experimental result with **15**, which failed to undergo rearrangement (Scheme 4). Unlike **S3**, the rearrangement of **S5** (or **15**) is hampered by an unfavorable electrostatic interaction between the ester and the nearby protecting group on the pyrrole in the TS (O···O = 3 Å, Figure 2).

Conversely, an ester group on the epoxide (**TS-S6**) lowers the barrier by 1.3 kcal/mol relative to **TS-S4**. This mirrors the effect of the ester in the simple divinyl epoxide **S3**. Electronically, the pyrrole and ester groups constitute a 1,4-acceptor/acceptor-substituted system; a similar synergistic effect of 1,4-diacceptor substitution in acyclic 1,5-dienes, which lowers the barrier for Cope rearrangement, has previously been described.[37]

Of the three pyrrole-containing TSs, **TS-S6** has the lowest barrier (27.8 kcal/mol). This is in accord with experiment, where **19** and **20** are the only vinyl pyrrole epoxides observed to undergo the Cope rearrangement. However, the barrier for **S6** is still 2 kcal/mol higher than that for parent divinyl epoxide **S1**, which rearranges at a lower temperature.[20] Based on the computed barriers for the three model vinyl pyrrole epoxides, epoxide **14** is predicted to rearrange 5 times more slowly than **19** or **20** at 150 °C, and **15** would rearrange 15 times more slowly, in both cases allowing competing reactions such as epoxide ring opening to dominate.

The calculations support the experimental results that demonstrated an ester group on the epoxide is important for the Cope rearrangement of vinyl pyrrole epoxides. Cope rearrangements of these substrates are intrinsically more difficult than those of simple divinyl epoxides. In addition, the ester group stabilizes the epoxide against ring opening, allowing for effective [3,3]-rearrangement. We are currently investigating this approach for the synthesis of the interesting natural products shown in Figure 1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02965.

Full experimental details, characterization data, copies of NMR spectra, computational details, and a complete citation for ref 32 (PDF)

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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(39) See the Supporting Information for details.

NOTE ADDED IN PROOF

The first total synthesis of MPC1001B, a member of the emestrin family, was reported after submission of this manuscript see: Kurogi, T.; Okaya, S.; Fujiwara, H.; Okano, K.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2015**, doi org/10.1002/ange.201507830.

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