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Design, Development, Mechanistic Elucidation, and Rational Optimization of a Tandem Ireland Claisen/Cope Rearrangement Reaction for Rapid Access to the (Iso)Cyclocitrinol Core

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Supporting Information

ABSTRACT: An approach to the synthesis of the (iso)cyclocitrinol core structure is described. The key step is a tandem Ireland Claisen/Cope rearrangement sequence, wherein the Ireland Claisen rearrangement effects ring contraction to a strained 10-membered ring, and that strain in turn drives the Cope rearrangement under unusually mild thermal conditions. A major side product was identified as resulting from an unexpected and remarkably facile [1,3]-sigmatropic rearrangement, and a tactic to disfavor the [1,3] pathway and increase the efficiency of the tandem reaction was rationally devised.

While it would be difficult to overstate the case that steroids have played an important role in the development of the field of synthetic organic chemistry, it would be equally fair to say that this describes, for the most part, an increasingly distant past era in the field of chemical synthesis. Occasionally, however, significant interest in steroid synthesis is rekindled by the discovery of fundamentally new steroid structural types,[1] and it was against this backdrop that Crews and Clardy et al. reported in 2003 the isolation and structure determination of isocyclocitrinol **1** and its C(22) acetate[2] as well as a structural revision of what had been an incorrectly assigned structure for cyclocitrinol **2**[3] (Figure 1).[4] Such novel

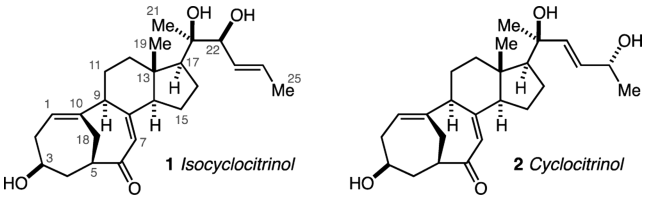

Figure 1. Isocyclocitrinol (**1**) and cyclocitrinol (**2**).

steroid skeletons are of inherent interest in chemical synthesis[5] to the extent that they inspire the development of new strategies and methods, while a step-economical synthetic entry into the cyclocitrinol core could facilitate more thorough explorations of the medicinal potential of these interesting structures.

The central synthetic challenge presented by the cyclocitrinols is the AB ring system, a [4.4.1]-bicycle with a bridgehead double bond instead of the familiar decalin. We began our retrosynthetic analysis with stripped down bicyclic ketone **3** and recognized that its corresponding potassium enolate **4** is the product of a hypothetical anionic oxy-Cope rearrangement[6] of [3.2.1]-bicycle **5** (Figure 2A). There are no

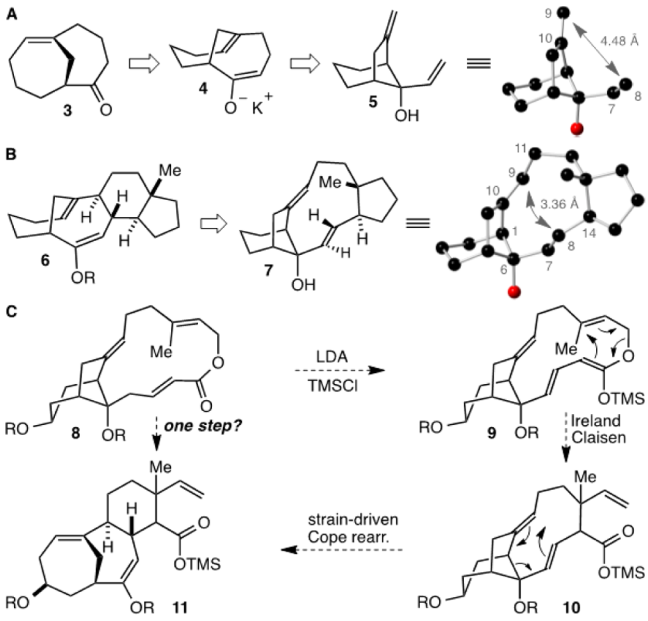

Figure 2. Retrosynthesis of (A) the AB bicyclic ring system by way of a hypothetical anionic oxy-Cope rearrangement and (B) the (iso)cyclocitrinol ring system by way of a strain-accelerated Cope rearrangement. (C) Proposal for a tandem Ireland Claisen/Cope rearrangement to rapidly establish the ABC core of the (iso)-cyclocitrinols.

known examples of this ring system undergoing a Cope rearrangement of any type,[7−9] and calculations[10] suggest that the termini of the alkenes (C(8) and C(9), cyclocitrinol numbering) in **5** are more than 4 Å apart when the vinyl group is oriented so as to allow for the necessary π overlap. By contrast, the same analysis applied to enol ether **6** leads to **7**, in which the two alkenes that must react are constrained within a 10-membered ring (Figure 2B). The calculated[10] structure for **7** reveals significant strain in the 10-membered ring that distorts

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the two alkenes (the C(1)−C(10)−C(9)−C(11) and C(6)−C(7)−C(8)−C(14) torsion angles are 156° and 157°, respectively) and forces them into the required chairlike alignment for the Cope rearrangement (C(8)−C(9) = 3.36 Å). It thus became our central hypothesis that if such a highly strained 10-membered ring could be prepared, it would undergo a strain-accelerated Cope rearrangement under unusually mild conditions. Among the approaches we considered for the synthesis of the 10-membered ring was the contraction of a larger, less-strained ring. Funk's approach to the strained bicyclic core of ingenol[11] by way of a ring-contracting Ireland Claisen rearrangement[12] served as a key inspiration and led us to target macrolactone **8** in the expectation that its conversion into silyl ketene acetal **9** would result in an Ireland Claisen rearrangement to give **10**, which would in turn undergo a strain-accelerated Cope rearrangement to give **11** (Figure 2C). The possibility that we might realize the single step transformation of **8** into **11** was enticing and provided the impetus to initiate this investigation.

Our investigations into the feasibility of the tandem Ireland Claisen/Cope rearrangement began with a version of macrolactone **8** that lacked the C(3) alcohol and was racemic (**12**,[13] Figure 3). Though initially disappointed to discover that

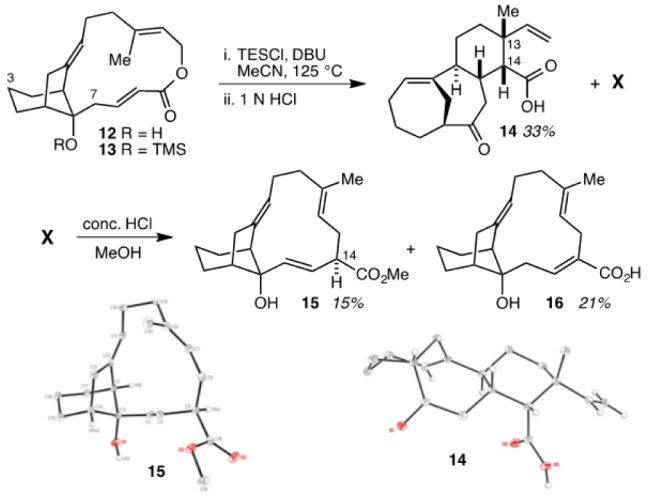

Figure 3. A demonstration of the feasibility of the tandem Ireland Claisen/Cope rearrangement in a model system and identification of the major side products.

traditional methods of silyl ketene acetal formation (e.g., LDA, TMSCl) led only to recovered starting material and decomposition (these experiments were carried out with substrate **13**), we were also not entirely surprised as the desired site of enolization (C(7)) is highly sterically hindered. We therefore examined the use of trialkylsilyl chlorides with the strongly basic yet sterically small amine 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) at elevated temperatures. After some experimentation, we found that treatment of **12** with triethylsilyl chloride (TESCl) and DBU in CH_3CN at 125 °C, followed by an acidic (1 N HCl) quench led to the isolation of carboxylic acid **14** in 33% yield. The structure of **14** was determined by single crystal X-ray diffraction, and this confirmed not only that the tandem Ireland Claisen/Cope rearrangement sequence had proceeded as planned but also, crucially, that the C(13) quaternary carbon stereocenter had been set with the correct configuration. A significant amount of nonpolar TES-containing material (**X**) was also obtained and this mixture was treated with conc. HCl in MeOH in an attempt to cleave all silyl groups. Two compounds were isolated from the resulting mixture, methyl ester **15** in 15% yield and acid **16** in 21% yield. The structure of **15** was determined by single crystal X-ray diffraction and facilitated the assignment of the structure of **16**. Thus, while this reaction did produce some of the desired product **14**, significant amounts of the 12-membered ring products **15** and **16** were also unexpectedly produced.

Following this demonstration of the viability of the tandem Ireland Claisen/Cope sequence, we developed a new approach to the synthesis of the macrolactone that both incorporated the C(3) alcohol and was highly enantioselective. The centerpiece of this approach is a tandem cross-metathesis/semipinacol rearrangement with vinyl epoxide **17** (prepared in 7 steps from (*R*)-epichlorohydrin) and alkene **18** to produce **19** as the major product of a 5:1 mixture of trisubstituted olefin isomers in 75% yield as previously described[14] (Figure 4). Three straightfor-

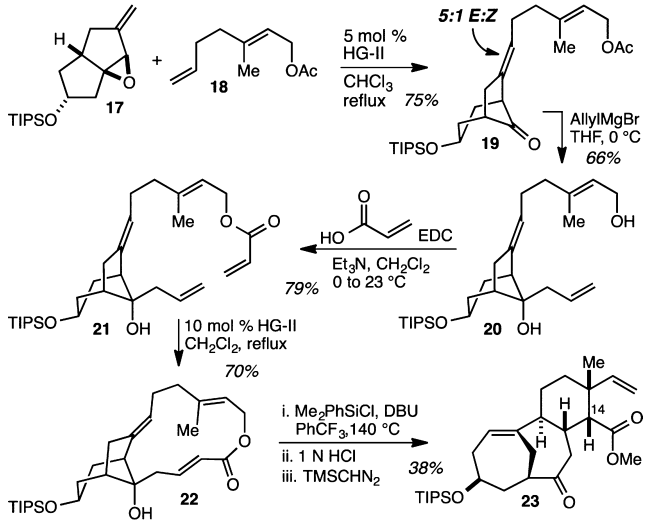

Figure 4. Five step conversion of **17** and **18** into **23** using two strain-driven tandem reactions.

ward steps (ketone allylation and acetate cleavage to give **20** (the olefin isomers were separated at this stage), alcohol acryloylation to give **21**, and ring-closing metathesis (RCM) with the second generation Hoveyda-Grubbs catalyst[15] (HG-II)) converted **19** into the requisite macrolactone **22**. Gratifyingly, **22** underwent the tandem Ireland Claisen/Cope reaction[16] to give **23** in 38% yield.[17] Thus, due to the development of two complexity-generating strain-driven tandem reactions, we had in this fashion realized the conversion of **17** and **18** into **23** in just 5 steps.

The identification of the 12-membered ring side-products (**15** and **16**) in the model series presented an opportunity to elucidate their mechanistic origin and in turn to design an improved variant of the low-yielding tandem rearrangement reaction. Consistent with the observed stereochemistry at C(13) and C(14) in **14**, we hypothesize that silyl ketene acetal **24** is formed from **12** and undergoes the Ireland Claisen rearrangement through the illustrated boat-like conformation to give **25**, which in turn undergoes the desired strain-accelerated Cope rearrangement to give **26** (Figure 5A). However, **25** has an alternative strain-relieving pathway available to it that leads

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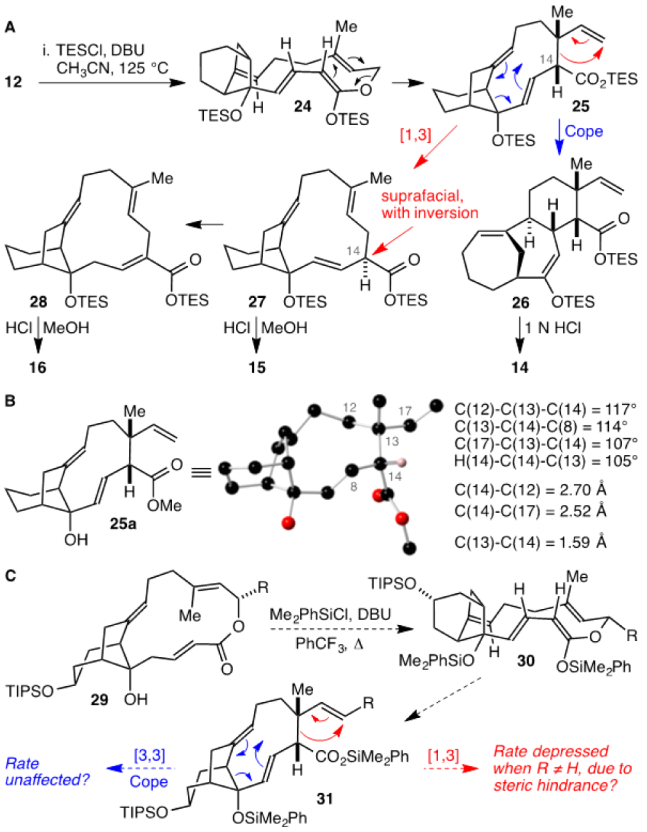

Figure 5. (A) Mechanistic model for the tandem Ireland Claisen/Cope rearrangement reaction. (B) The calculated structure for **25a** reveals significant strain that favors an unusual [1,3]-rearrangement pathway. (C) Proposal for a simple way to disfavor the undesired [1,3]-rearrangement and thereby increase the efficiency of the tandem Ireland Claisen/Cope rearrangement.

to **27** (**15** after methanolysis/esterification), some of which isomerizes to **28** (**16** after methanolysis) under the harsh reaction conditions (DBU at 125 °C). That this alternate pathway is a rare example of a [1,3]-sigmatropic rearrangement was indicated by the inverted C(14) stereochemistry in the X-ray structure of **15**, as such rearrangements are allowed in a concerted suprafacial sense only if the migrating carbon center undergoes inversion as elegantly demonstrated by Berson.[18] Intrigued by the remarkable facility of this [1,3] rearrangement,[19] we calculated[10] the structure of **25a** (Figure 5B). Notable features of this structure include a small but significant expansion of the C(12)−C(13)−C(14) and C(13)−C(14)−C(8) bond angles and a small but significant contraction of the C(17)−C(13)−C(14) and H(14)−C(14)−C(13) bond angles and a significant lengthening of the migrating C(13)−C(14) bond (1.59 Å). These data suggest that the facility of the [1,3]-rearrangement is due to a weakened and polarized (at the extreme to an enolate and a tertiary allylic carbocation) C(13)−C(14) bond which results in increased electron density behind C(14) and to the ring-strain which manifests itself by pushing the vinyl group closer to the backside of the C(13)−C(14) bond. As well, it is likely that the C(14) diastereomer, had we obtained it, would not be able to do the [1,3]-rearrangement because the ester would sterically preclude C(14) "rolling" over as it migrates to the other end of the vinyl group.[20] We thus appear to have unwittingly stumbled upon a system that is about as perfectly set up for a [1,3]-rearrangement as possible.

Having developed this mechanistic model, we were in a position to devise a way to disfavor the undesired [1,3]-rearrangement pathway. To that end, the potential impact of substitution of the pro-*S* proton on the acyloxy allylic carbon with an alkyl group as in **29** (R = alkyl) was evaluated (Figure 5C). Such a substituent would be expected to occupy a pseudoequatorial position on the boat-like Claisen rearrangement pathway as in **30** and would therefore be expected to have a minimal impact on the Claisen rearrangement, and, since the R group is quite remote, on the Cope rearrangement of **31**. By contrast, it seemed reasonable to expect that the R group in **31** might depress the rate of the undesired [1,3]-rearrangement pathway due to steric hindrance. In this fashion, we hypothesized that as R becomes larger, the efficiency of the tandem Ireland Claisen/Cope sequence would increase correspondingly.

The requisite modified cross-metathesis substrate **32** (R = *i*-Pr) was prepared (using Nugent's modification[21] of the Noyori protocol[22] for the enantioselective addition of dialkylzinc reagents to aldehydes—see the Supporting Information for details) and subjected to the tandem cross-metathesis/semipinacol rearrangement reaction with epoxide **17** (Figure 6).

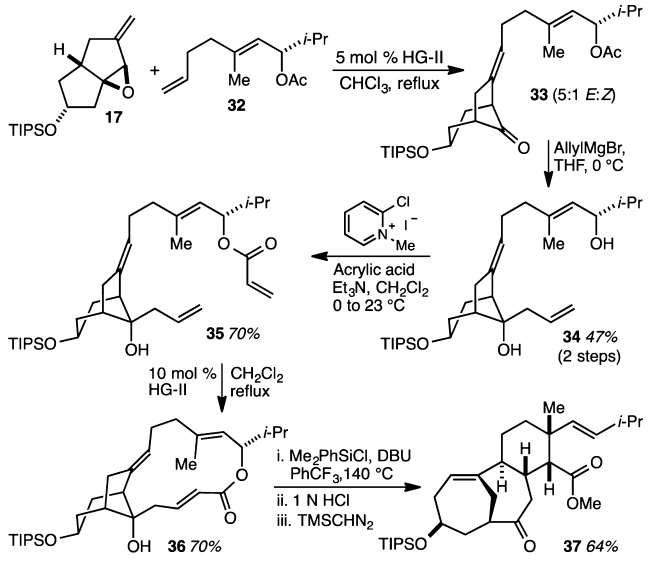

Figure 6. Substitution of the pro-*S* allylic position disfavors the [1,3]-rearrangement and significantly increases the efficiency of the tandem Ireland Claisen/Cope rearrangement.

The reaction proceeded smoothly and led to the isolation of **33** as a 5:1 *E*:*Z* mixture. As above, treatment of **33** with allylmagnesium bromide resulted in both diastereoselective ketone allylation and acetate cleavage. Separation of olefin isomers was possible at this stage and **34** was isolated as a single compound in 47% yield over two steps. Secondary alcohol acryloylation using 2-chloro-1-methylpyridinium iodide and RCM also proceeded as above and led to acrylate ester **35** and macrolactone **36**. Gratifyingly and consistent with our mechanistic analysis, subjection of **36** to the tandem Ireland Claisen/Cope reaction led to the isolation of **37** in 64% yield. This deceptively simple and rationally designed addition of an *i*-Pr group thus led to a dramatic improvement in the efficiency of the tandem reaction sequence (38% for **23** vs. 64% for **37**).

We have developed an efficient approach to the core ring system of the (iso)cyclocitrinols. The key step is a tandem ring-

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contracting Ireland Claisen/Cope rearrangement sequence that, in combination with the tandem cross metathesis/semipinacol rearrangement, allows the conversion of **17** and **18**/**32** into **23**/**37** in just five steps. Through a careful mechanistic analysis, the origin of the side products in the tandem Ireland Claisen/Cope rearrangement reaction was found to be an unexpected and surprisingly facile [1,3]-sigmatropic rearrangement that is in competition with the desired Cope rearrangement. A simple method to disfavor the undesired [1,3]-rearrangement reaction was devised based on this mechanistic model, and this led to a significant increase in the efficiency of the tandem Ireland Claisen/Cope rearrangement reaction. While it is possible to imagine simply excising the "R" group in **37** after it has fulfilled its purpose, our current efforts are focused instead on devising a new "R" group for **29** that will not only perform the function of impeding the [1,3]-rearrangement reaction but also be comprised of functionality that will be useful for the rapid introduction of the C(17) side chain with the proper configuration.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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