Syntheses of CP-225,917 and CP-263,114

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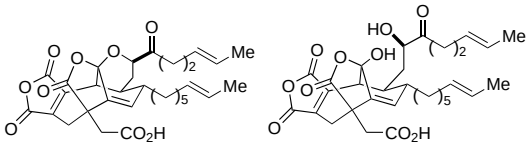
The synthesis of complex structures provides a stringent test of known methods, and when these fail, the endeavor challenges the modern synthetic chemist to innovate. The isolation and structure elucidation of novel natural products provides an important well-spring of challenges that can drive the development and study of reaction chemistry. Research programs aimed at the synthesis of structurally complex natural products thus can lead to the discovery of novel reaction methods, as well as the development of innovative strategies for molecular synthesis. Historically there have been natural products that have especially piqued the imagination of chemists. The study of the syntheses of these important natural products provides in-depth chronological evaluation of the field of organic synthesis, highlighting the important advances in the science, as well as the remaining gaps that require additional work.[1]

The recent isolation of CP-263,114 (**1**) and CP-225,917 (**2**) adds to the lineage of natural products that pose daunting synthetic problems, leading to opportunities for much discovery and innovation. These fungal metabolites were documented by Pfizer as part of a program aimed at identifying novel, powerful inhibitors of squalene synthetase, as well as farnesyl transferase.[2] Inhibitors of these enzymes have proven useful in the development of potential cholesterol-lowering agents and anticancer chemotherapeutics.[3] These intriguing metabolites made their appearance in the wake of another class of novel, structurally unusual squalene synthetase inhibitors, namely, the zaragozic acids, which have been of broad interest in the pharmaceutical industry.[4]



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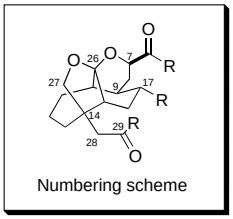
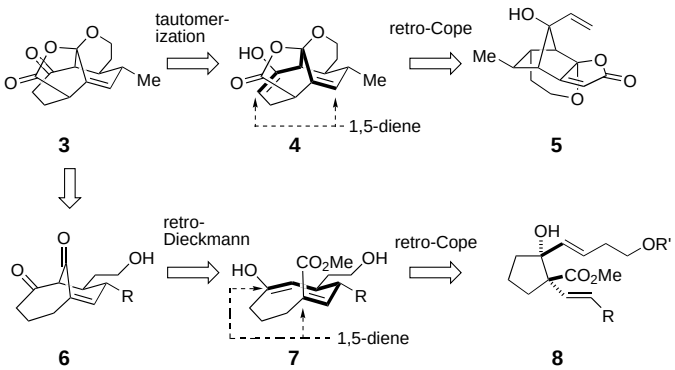


The polycyclic array found in CP-263,114 (**1**) and CP-225,917 (**2**) possesses daunting stereochemical and structural complexity that provides challenging problems in molecular synthesis, including an anti-Bredt bridgehead olefin along with a collection of unusual, densely packed, labile functional groups. It is not surprising that these structures have piqued the imagination of many research groups worldwide producing a number of elegant, creative approaches. The most prominent contributions include those by the groups of Armstrong,[5] Clive,[6] Danishefsky,[7] Fukuyama,[8] Leighton,[9] Nicolaou,[10] and Shair.[11] Recently, the efforts of two of these groups, those of Nicolaou and Danishefsky, have culminated in successful total syntheses. The diverse strategies that have been reported by these groups attest to the power and vitality of organic synthesis and validate the fact that natural products synthesis programs offer a unique way to discover and invent novel, interesting reactions that directly address specific problems in synthesis (see also Lit. [1]).

Shair et al. and Leighton et al. have independently reported two innovative strategies en route to this class of natural products. These approaches are based on retrosynthetic analyses consisting of two different oxy-Cope rearrangements (Scheme 1). In the Leighton analysis, enone **3** is accessed from



3 **4** **5**

6 **7** **8**

Scheme 1. Leighton's and Shair's (top and bottom, respectively) retrosynthetic strategies for the CP molecule core bicycle.

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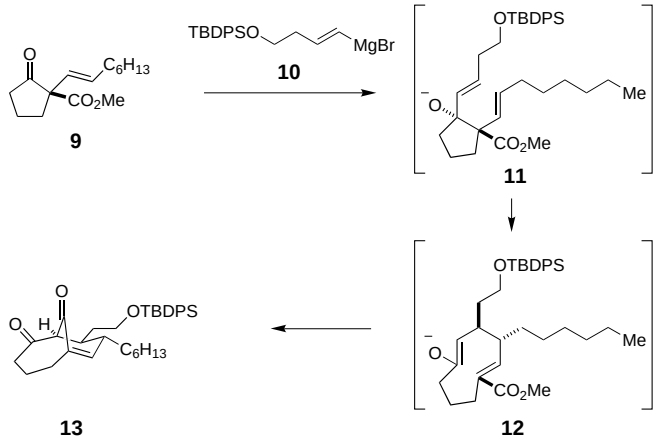
a suitable 1,5-diene **4** by an oxy-Cope rearrangement (**5** to **4**). In the Shair route, the bridgehead ketal is retrosynthetically converted into the corresponding ketone, wherein the resulting 1,3-dicarbonyl relationship serves as the keying element for a retro-Dieckmann disconnection (**6** to **7**). The resulting enone (shown as its enol tautomer **7** in Scheme 1) immediately suggests assembly by oxy-Cope rearrangement (**8** to **7**). The successful implementation of these oxy-Cope rearrangements in both strategies allows considerable efficiency in the assembly of the CP core. In addition, the application of these molecular rearrangements within a sequence of tandem reactions lends further efficiency to each of the strategies.

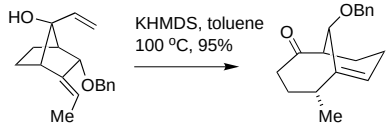
The Shair approach commences with the nucleophilic addition of **10** to cyclopentenone **9**, leading to the formation of **11** (Scheme 2). This 1,5-diene is ideally functionalized as a



Scheme 2. The one-pot oxy-Cope rearrangement and Dieckmann reaction reported by Shair et al. for the synthesis of the model bicycle **13**. TBDPS = *tert*-butyldiphenylsilyl.

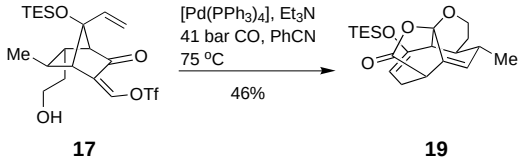
substrate for an anion-accelerated oxy-Cope rearrangement to afford enolate **12**. The enolate intermediate undergoes Dieckmann cyclization affording the desired functionalized CP bicyclic core **13**. In the experiment, when **9** was treated with **10**, diketone **13** was isolated directly from the reaction mixture in an impressive 64% yield.

The Leighton synthesis commences with keto ester **15** which is readily prepared following a previously reported route from diene **14** (Scheme 3).[12] In eight steps, **15** is converted into ketone **16** which functions as a critical precursor to the substrate for the oxy-Cope rearrangement. Treatment of **16** with KHMDS and methyl formate provided a vinyl alcohol that was subsequently transformed into the corresponding vinyl triflate, which was then desilylated to give **17**. A Pd-catalyzed carbonylation reaction then furnished lactone **18**. When **18** was heated in toluene at reflux for one hour, the expected Cope rearrangement occurred and **19** was isolated in excellent yield. Leighton speculates that the inherent strain of lactone **18** resulted in a significant rate acceleration over a similar rearrangement that had been reported by Clive in an independent approach to a model of the CP core [Eq. (1)].



(1)

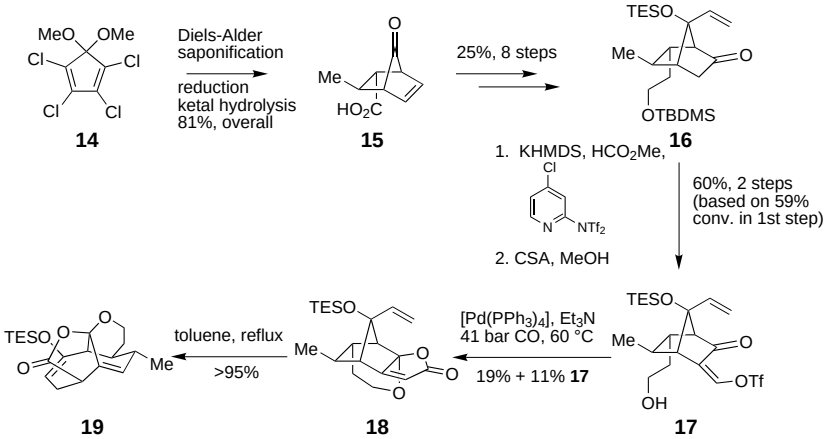
Having established the viability of their bold strategy, Leighton and co-workers examined the possibility of effecting the conversion of vinyl triflate **17** to the rearranged structure **19** by conducting the Pd-catalyzed carbonylation reaction and subsequent Cope rearrangement sequentially in a single pot [Eq. (2)]. Indeed, this strategy was successfully implemented;



(2)

thus, treatment of **17** with CO (41 bar) in the presence of $[Pd(PPh_3)_4]$ in benzonitrile (75–110 °C) furnished **19** directly in a remarkable 46% yield (compared to 19% yield in the stepwise version).

The focal point of the Nicolaou strategy that lead to the successful total synthesis of CP-225,917 (**2**) and CP-263,114 (**1**) is the assembly of the requisite [4.3.1] core through an unusual Diels–Alder reaction, wherein **20** undergoes intramolecular cycloaddition to afford **21** in the presence of Me_2AlCl catalyst (15 mol%) in an impressive 90% yield (Scheme 4). In a related study, Fukuyama has independently reported a similar cycloaddition reaction, albeit on a model system [Eq. (3)].[8] The fact that **20** is prepared in only 13 steps and that the cycloaddition reaction proceeds in high yield, allowed Nicolaou and co-workers to readily prepare multigram quantities of this key, advanced intermediate. This point is not to be underestimated, as the unusual juxtaposition of



Scheme 3. Synthesis of tetracyclic model compound **19** by Leighton et al. TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, KHMDS = potassium bis(trimethylsilyl)amide, CSA = camphorsulfonic acid, Tf = trifluoromethanesulfonyl.

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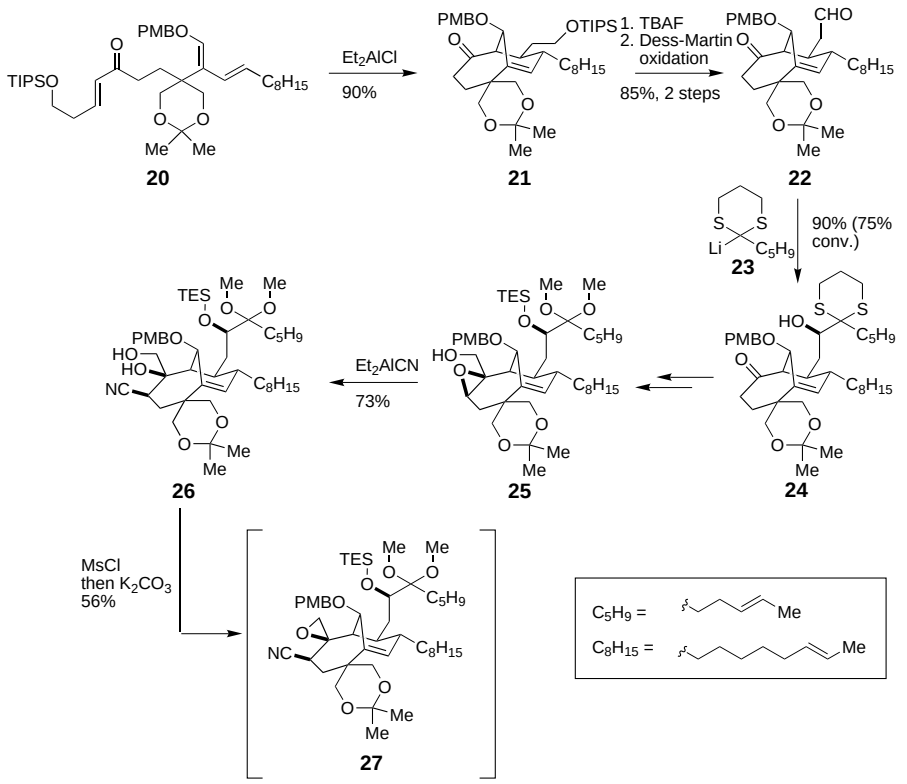
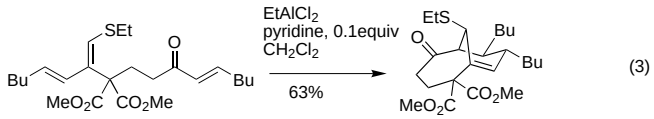


Scheme 4. Early steps of the total synthesis by Nicolaou et al. including intramolecular Diels–Alder construction of the core bicycle and subsequent side-chain elaborations. TIPS = triisopropylsilyl, PMB = *para*-methoxybenzyl, Ms = methanesulfonyl, TBAF = tetrabutylammonium fluoride.



(3)

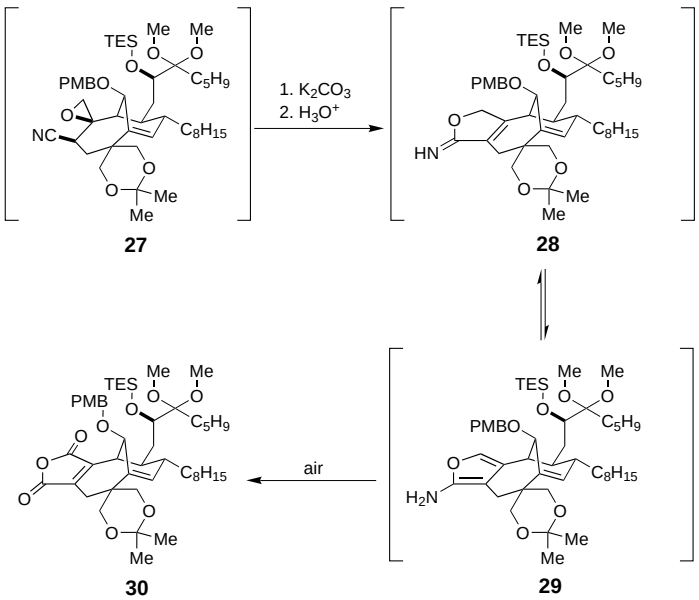
functionality in C-263,114 (**1**) and CP-225,917 (**2**) assured challenging steps further along the route which would necessitate an efficient route that would provide large quantities of advanced densely functionalized intermediates for study.

One of the first remarkable discoveries after the preparation of the bicyclic system following oxidation of **21** to afford **22** was that the addition of lithium dithiane **23** to aldehyde **22** proceeds in 11:1 diastereoselectivity to give the desired adduct **24**. This impressive level of diastereoselectivity may be related to similar results that have been independently documented by Danishefsky and co-workers in their elegant study of the epimerization chemistry of CP-225,917 and CP-263,114 (vide infra). In that study Danishefsky et al. observed a similarly strong and unexpected stereochemical bias imparted by the surrounding ring system in the context of an epimerization study of this stereocenter. These unanticipated results attest to the curios to be discovered in a complex molecule synthesis.

In the synthesis of Nicolaou et al., the subsequent installation of the anhydride of the CP core provided additional surprises. Treatment of **25** with Nagata's reagent (Et_2AlCN) lead to product **26** which is formally derived from an unexpected *syn* epoxide-ring-opening reaction. Diol **26** was subsequently subjected to cyclodehydration conditions to furnish cyano-epoxide **27**. Epoxide **27** underwent a remarkable series of cascade reactions to directly provide anhydride **30**. Thus, following treatment with base and then acid under an oxidizing atmosphere (air) anhydride **30** was isolated in 56% yield (Scheme 5).

Despite the fact that a sizeable portion of the structure had been masterfully assembled at this point in the route, the synthetic obstacles remaining were significant. These included the necessary homologation at C28, oxidation at C27, and the installation of the bridgehead ketal.

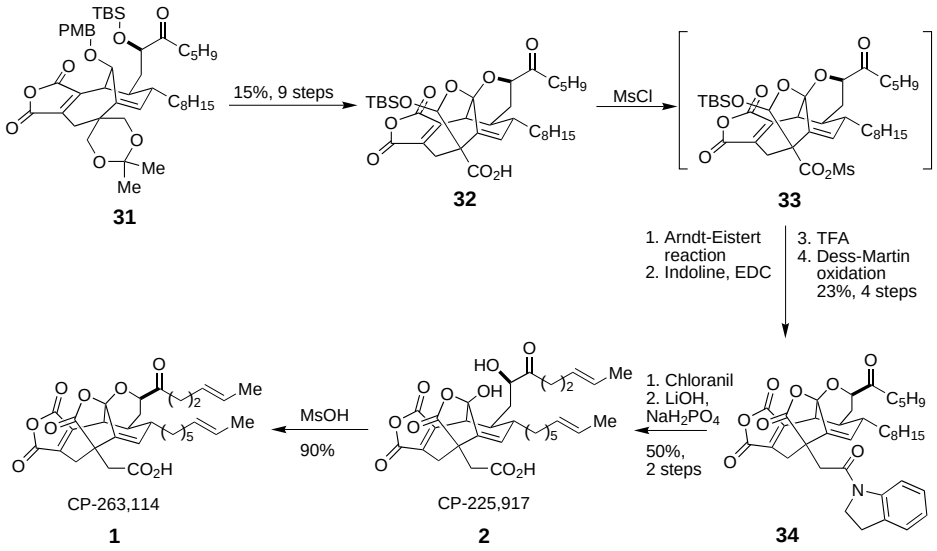
The completion of the synthesis was possible as a consequence of the development of new reaction methodology and careful strategic planning. The requisite oxidations required clever timing of the oxidation and ring-closing sequences as a series of investigations had revealed a number of troublesome side reactions of this densely functionalized bicyclic ring system. Straightforward protecting group manipulation provided **31**



Scheme 5. One-pot conversion of cyanoepoxide **27** to the requisite anhydride **30** in 56% overall yield by Nicolaou et al.

which, through a carefully orchestrated series of reactions was transformed into **32** (Scheme 6). This intermediate appropriately masks the C27 alcohol and allows selective oxidative manipulation as the corresponding lactol.

Homologation at C28 proved to be a challenge as a consequence of the highly hindered nature of this carboxyl group. In this regard, standard methods for carboxyl activa-



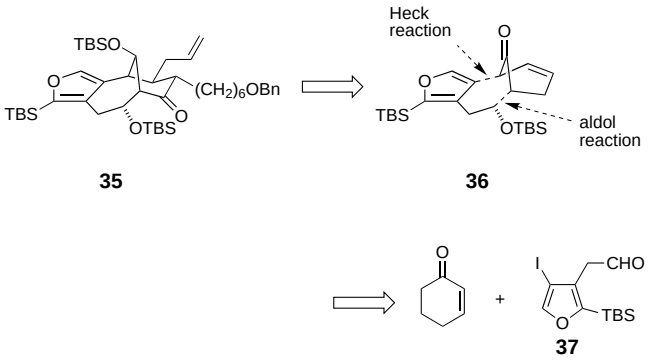
Scheme 6. Final steps of the total syntheses by Nicolaou et al. EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride.

The strategy pursued by Danishefsky and co-workers is based on a retrosynthetic analysis which efficiently dissects the bicyclic core into two simple fragments, furan **37** and 2-cyclohexenone (Scheme 7). This plan was elegantly and efficiently realized in an approach that provides ready access to a variety of compounds incorporating the critical bicyclic core with varied side-chains.

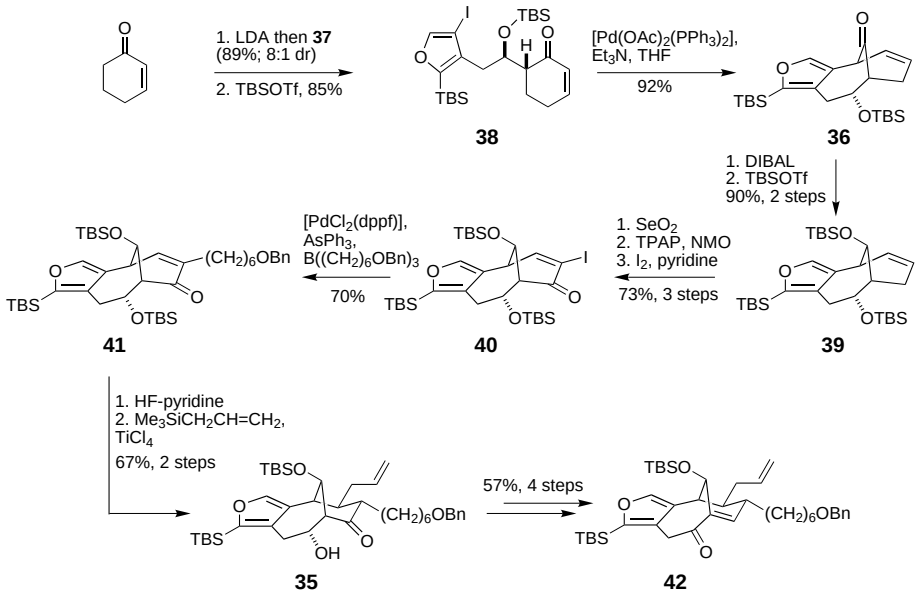
The Danishefsky synthesis commenced with the aldol addition between 2-cyclohexenone and **37** to afford adduct **38** in high yield and good diastereoselectivity (8:1) (Scheme 8). The stage was set for subsequent ring closure to afford the desired bicyclic ring

tion that have been employed for the Arndt–Eistert homologation reaction proved unsuccessful. Nicolaou and co-workers subsequently devised a novel strategy for the activation of such hindered carboxylic acids. It was established that the hindered carboxylic acid in **32** could be converted into the corresponding acyl mesylate **33** which in turn would react with diazomethane. The intermediate diazoketone undergoes a Wolff rearrangement to give the desired acetic acid side-chain which is subsequently condensed with indoline to afford amide **34**. A methodological study of carboxyl activation by preparation of the corresponding mixed anhydride has revealed the unique aspects of this strategy and its general application to the preparation of hindered acyl mesylates.[10d]

It was necessary to protect the C29 carboxyl group as an amide in the final stages of the approach in order to close the final ring through the formation of the ketal at C26. The decision to employ an indoline amide as a protecting group for the C29 carboxylic acid was based on unsuccessful use of an aniline amide. In this regard, the acyl anilide was found to undergo oxidation and then participate in an intramolecular cycloaddition reaction with the bridgehead olefin. By contrast the indoline amide did not undergo deleterious oxidation and yet was amenable to subsequent removal under remarkably mild conditions. Thus, in the final steps of the synthesis, chloranil oxidation of the indoline followed by LiOH hydrolysis gave CP-225,917 (**2**). Following treatment with methanesulfonic acid, CP-225,917 (**2**) was converted into CP-263,114 (**1**).



Scheme 7. Danishefsky's retrosynthetic analysis. An aldol reaction and a Heck reaction are key bond-forming steps in the synthesis of the bicyclic core.



Scheme 8. Early steps in the synthesis by Danishefsky et al. including the key aldol and Heck reactions and incorporation of side-chain precursors. TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine-*N*-oxide, LDA = lithium diisopropylamide, DIBAL = diisobutylaluminumhydride, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

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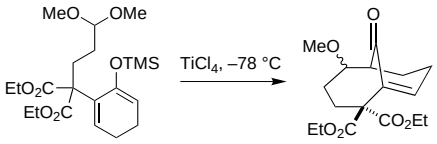
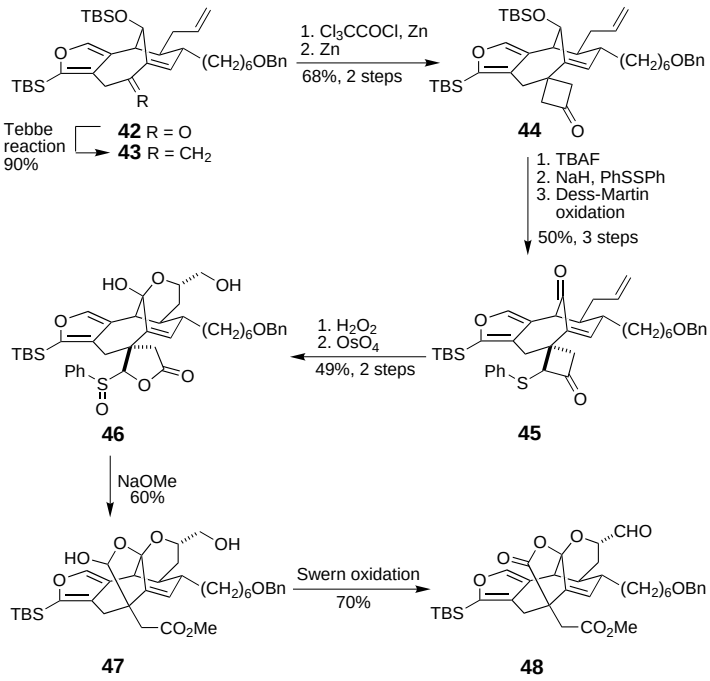
system. When **38** was subjected to Heck conditions the product **36** of an intramolecular vinylation reaction was isolated in 92% yield. The combination of these two steps assembled the bicyclic system in an efficient and convergent manner allowing a straightforward synthesis of the natural product. The fused furan ring serves as a mask for the anhydride that will be revealed late in the synthesis, and the olefin in **36** is ideally positioned for subsequent elaboration of the cyclohexyl ring. In an independent study of a model system en route to the synthesis of the CP core, Armstrong has documented a related aldol cyclization reaction that gives rise to the [4.3.1] bicyclic CP core [Eq. (4)].



(4)

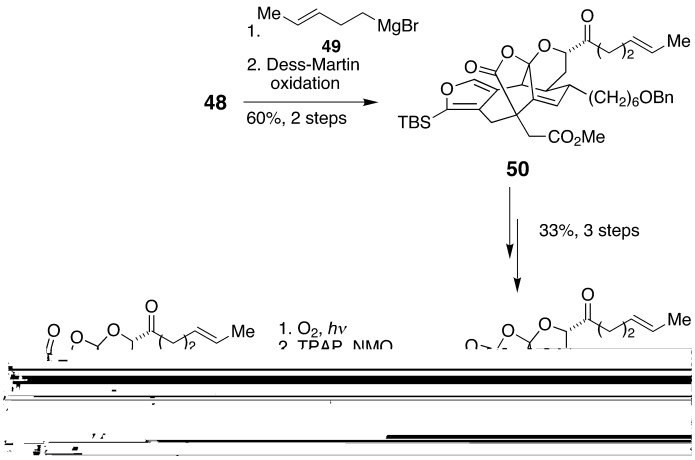
Functionalization at the endocyclic olefin by treatment of **39** with SeO_2 effected allylic oxidation and yielded an intermediate alcohol that was subsequently oxidized to the corresponding unsaturated ketone; this was iodinated to give vinyl iodide **40**. A Suzuki coupling reaction with the C17 side-chain then efficiently provided **41**. Although direct conjugate addition to enone **41** proved difficult, it was observed that the corresponding desilylated enone readily undergoes a Sakurai conjugate addition reaction in excellent yield to give adduct **35** with the desired *trans* stereochemical relationship at C17 and C9. The bridgehead alkene was then installed through selective manipulation of the hydroxyl and keto functionalities followed by a dehydration reaction.

Installation of the critical C14 carboxyl side-chains was accomplished by a cyclobutane ring fragmentation reaction (Scheme 9). When ketone **42** was subjected to the Tebbe olefination reaction conditions alkylidene **43** was formed in 90% yield. Reaction of this olefin with dichloroketene afforded the corresponding dichlorocyclobutanone. Reductive removal of the geminal dichloro substituents gave **44** which underwent regioselective enolization and reaction with PhSSPh to give the corresponding substituted cyclobutanone. The importance of this substitution in controlling the selectivity in a subsequent Baeyer–Villiger oxidation, as well as a fragmentation reaction of the resulting lactone in this strategy, had been the subject of exploratory studies by the Danishefsky group. The overall transformation of the cyclobutanone proved to be ideally executed when the sulfoxide was employed. Thus, Baeyer–Villiger oxidation was followed by oxidation of the sulfenyl lactone to the corresponding sulfoxide. Following chemoselective dihydroxylation of the monosubstituted alkene in the C9 side-chain, the secondary alcohol is proposed to participate in a cascade of rearrangements mediated by NaOMe to give lactol **47** incorporating the remaining two rings found in the CP core. Oxidation of **47** then furnished lactone **48**, an important intermediate in the successful completion of the synthetic route and in accompanying studies.



Scheme 9. Formation of the pyran and lactone rings in the Danishefsky route.

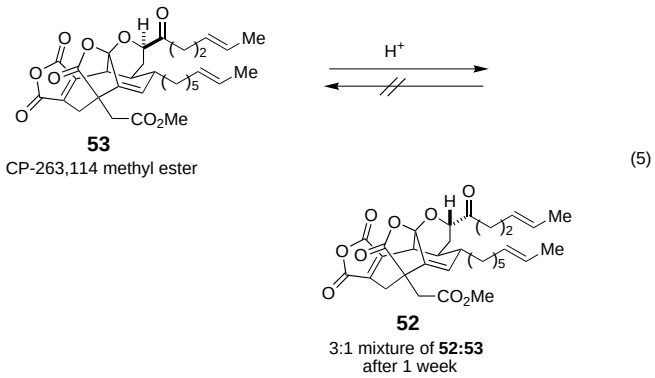
Elaboration of aldehyde **48** allowed for installation of the C7 side-chain through a two-step sequence: aldehyde addition and Dess-Martin oxidation (Scheme 10). Finally, the anhydride which had been successfully masked throughout the synthesis as a furan, could be revealed by oxidation of the heterocycle. Thus, following elaboration of the C17 side-chain, treatment of furan **51** with singlet oxygen followed by oxidation of the resulting lactol (Ley oxidation) afforded the methyl ester **52**.



Scheme 10. Late-stage addition of the C1–C5 side chain and conversion of the furan to the maleic anhydride residue.

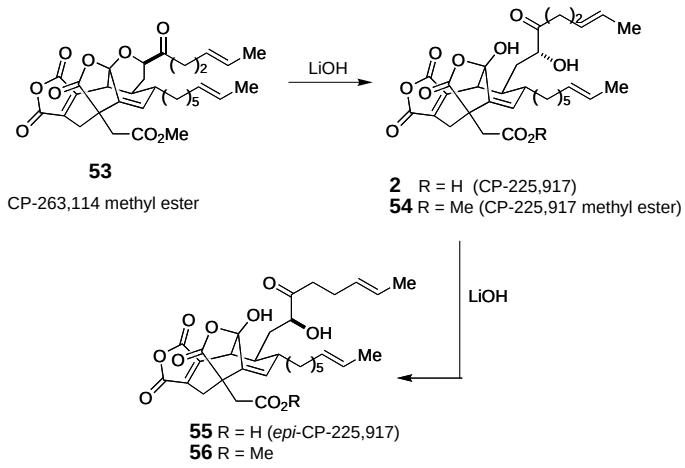
At this point in the synthesis, comparison of the synthetic material **52** to the methyl ester of the authentic natural product **53** led these investigators to conclude that the compounds differed with respect to the configuration at C7. A series of elegant studies revealed intriguing issues concerning epimerization of this stereogenic center, raising the

interesting postulate that the epimeric material that had been accessed by total synthesis (**52**) may also be a natural product. In this regard, when **53**, the methyl ester of CP-263,114, was subjected to acidic conditions an approximate 3:1 mixture of **52** and **53** was obtained, indeed favoring the 7*S* epimer [Eq. 5]. However, attempted equilibration of **52** to **53** was not successful, leading to either extensive decomposition of **52** or its re-isolation.



(5)

Danishefsky and co-workers next conducted a meticulous study with CP-225,917 (**2**) and its methyl ester **54** in an effort to probe whether this ring-opened CP structure would be prone to epimerization at C7. Treatment of **2** with LiOH gave a 1:1 mixture of **2** and **55** (Scheme 11). Analogous experiments could be conducted with the corresponding methyl ester **53**, giving a 1.7:1 mixture of ring-opened structures epimeric at C7. These investigators subsequently demonstrated that the "closed" and "open" forms **53** and **54**, respectively, could be interconverted under alkaline conditions without attendant epimerization at C7, utilizing a procedure initially disclosed by the Pfizer workers. The methyl ester **54** of CP-225,917 could then undergo epimerization to give **56**, epimeric at C7 incorporating the 7*S* configuration. Through further studies, these workers established that the "synthetic" 7*S* configuration was considerably more stable than the "natural" 7*R* configuration of the initially reported compounds, CP-263,114 (**1**) and CP-225,917 (**2**). When the epimeric synthetic material **52** was subjected to the epimerization regime (alkaline opening, and epimerization, followed by ring closure) and an ester hydrolysis, **1** could be detected, albeit in trace quantities. It is noteworthy that in contrast to the ready epimerization of the natural 7*R* epimers (open and closed forms) the synthetic 7*S* epimeric series does not participate in efficient isomerization reactions. In addition to revealing the remarkable natural product chemistry of these substances, the investigators noted the presence of the C7 epimers in the fermentation broths, a feature that had not been previously appreciated.



Scheme 11. Results of the C7 epimerization studies by Danishefsky et al.

The impressive creativity, ingenuity, and tenacity exhibited in the synthetic efforts towards CP-263,114 (**1**) and CP-225,917 (**2**) underline the power of the modern synthetic chemist when faced with such daunting challenges. The work by Armstrong, Clive, Danishefsky, Fukuyama, Leighton, Nicolaou, and Shair discussed in this highlight underscores the important discoveries and innovations that target-oriented natural products synthesis projects can yield.

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In Spite of the Chemist's Belief: Carbonic Acid Is Surprisingly Stable

Ralf Ludwig* and Andreas Kornath*

It is conventional wisdom in any chemistry textbook that carbonic acid is kinetically unstable. Accordingly, the recently published Encyclopedia of Inorganic Chemistry[1] still claims: "Pure carbonic acid, H_2CO_3, cannot be isolated because of its ready dehydration to carbon dioxide, CO_2." Despite belief in the nonexistence of carbonic acid, chemists succeeded in recognizing its stability in the last few years. They were able to synthesize carbonic acid at low temperatures by high-energy irradiation of cryogenic carbon dioxide/water ice mixtures[2, 3], proton-irradiation of pure solid CO_2[4] and by protonation of bicarbonate[5, 6]. The resulting carbonic acid was characterised by IR spectroscopy and mass spectrometry. Recently Liedl and coworkers[7] explained in a beautiful theoretical work why carbonic acid can exist in its free form and why chemists thought and taught for so long that this compound is unstable.

Carbonic acid is of special importance in biological and geochemical carbonate-containing systems. The equilibrium of carbonic acid with carbon dioxide and water and its significance are well recognized and carefully studied. Despite the reaction [Eq. (1)] making carbonates the most abundant minerals on earth, carbonic acid is difficult to observe spectroscopically in its free state.

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \quad (1)$$

Carbonic acid is known to be present to the extent of about 0.003 % in water containing dissolved CO_2. The dissociation constant of carbonic acid is large in comparison with those of other hydrates. This has been understood as a result of the high stability of the unhydrated species, CO_2. However, an activation energy of 15.5 kcal mol^{-1} [8] for the dissociation reaction of carbonic acid to water and carbon dioxide suggested that it should be possible to observe carbonic acid in its free state.

In fact, there had been two claims of the preparation of free carbonic acid as an etherate, but no spectral evidence was provided. Isolation of such an ether complex was achieved by the addition of an etheral solution of anhydrous hydrogen chloride to a suspension of finely crushed sodium bicarbonate in ether at 243 K.[9] Cooling the solution to 195 K resulted in the precipitation of a white crystalline etherate. In a similar procedure Gattow and Gerwath[10] used dimethyl ether and sodium carbonate at 238 K to prepare the dimethyl ether complex of carbonic acid. They obtained a solid which decomposed violently above 278 K, yielding water, carbon dioxide and ether. For both studies NMR and IR spectra were not obtained.

For a long period, carbonic acid had not been detected by any spectroscopic means; its formation was only inferred from kinetic data. Schwarz et al.[11] first demonstrated the existence of carbonic acid as a stable, discrete species. Thermal decomposition of NH_4HCO_3 gave carbonic acid in the gas phase which was detected by neutralization–reionization mass spectroscopic (NR-MS) techniques. Olah et al.[12] found spectral evidence for carbonic acid by calculating ^{13}C chemical shifts and comparing them with those obtained from NMR measurements under superacidic conditions. In this environment, the carbonic acid and its protonated species is present in an equilibrium [Eq. (2)].

$$C(OH)_3^+ + HF \rightleftharpoons H_2CO_3 + H_2F^+ \quad (2)$$

Recently, the protonated carbonic acid was prepared in superacids (HF/AsF_6, HF/SbF_6) from carbonic acid bis(trimethylsilyl)ester.[13] The salts have been characterized with vibrational spectroscopy and X-ray analysis. Obviously, the protonated carbonic acid is formed under these conditions in situ by cleavage of the silyl ester.

The analysis of the IR and mass spectral data by Moore and Khanna[2] gave strong evidence for the formation of carbonic

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