Article

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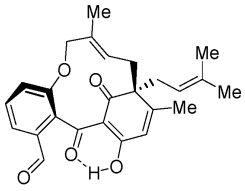

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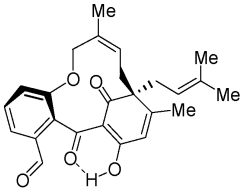

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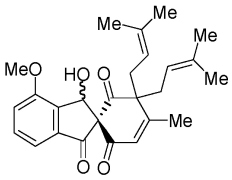

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The Total Synthesis of Coleophomones B, C, and D

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Abstract: Members of the coleophomone family of natural products all possess several intriguing and challenging architectural features, as well as exhibit unusual biological activity. They, therefore, constitute attractive targets for synthesis. In this Article, we describe the total synthesis of coleophomones B (**2**), C (**3**), and D (**4**). The highly strained and congested 11-membered macrocycle of coleophomones B (**2**) and C (**3**) was constructed using an impressive olefin metathesis reaction. Furthermore, both of the requisite geometric isomers of the $\Delta^{16,17}$ within the macrocycle could be accessed from a common precursor, facilitating a divergence that lent the coleophomone B (**2**)/C (**3**) synthesis an unusually high degree of efficiency. The synthesis of coleophomone D (**4**) confirmed that it exists as a dynamic mixture of isomeric forms with a different aromatic substitution pattern from the other family members.

Introduction

In 1998, a Japanese patent[1] was issued on behalf of the Shionogi Pharmaceutical Co., in which the structures of three new and unique secondary metabolites (**1**−**3**, Figure 1) were disclosed. These naturally occurring diterpenes, at this stage assigned only alphanumeric codes to identify them, had been isolated from a *Stachybotrys cylindrospora* fungal broth. They had become the subject of a patent due to the interesting biological activities that they possessed, including antifungal action and the ability to inhibit the serine protease enzyme, heart chymase, which is responsible for converting angiotensin I to angiotensin II.[2] This latter property endowed the compounds with significant potential as leads for development programs targeting drugs to treat hypertension and congestive heart failure.

One year later, a second patent[3] appeared from the same company revealing that there was a fourth sibling, a compound (**4**) which existed in a state of flux between different isomeric forms (Scheme 1). This last member of the family to be identified had been isolated from another *Stachybotrys* broth (*Stachybotrys parvispora Hughes*), and it showed biological activity analogous to that of the other congeners.

Later, in 2000, details regarding some of these interesting fungal metabolites reached a broader audience when a drug discovery team from Merck published an account in a mainstream chemical journal of their isolation of coleophomones A (**1**) and B (**2**).[4] This team, apparently unaware of the existing patent coverage of these compounds, had isolated them from a *Coleophoma* sp fungal broth produced using samples collected in the Sierra Villuercas in Spain, hence, the rationale in naming the isolates the coleophomones. In this case, the compounds had been identified as the result of an antibacterial assay, the origin of their weak antibacterial activity being traced to the inhibition of a crucial bacterial transglycosylase enzyme. For

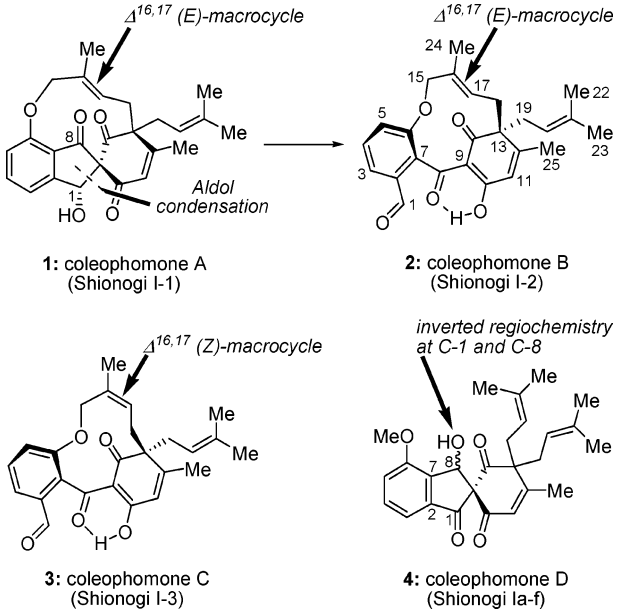

Figure 1. Structures of coleophomones A−D (**1**−**4**).

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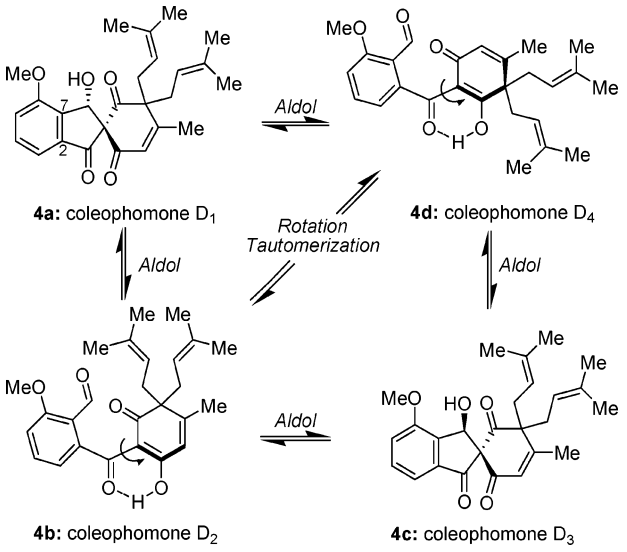
(1) Kamigakinai, T.; Nakashima, M.; Tani, H. Japanese patent JP 10101666 A2, 1998 [CAN 129:589 AN 1998:236773].
(2) Urata, H.; Kinoshita, A.; Misono, K. S.; Bumpus, F. M.; Husain, A. *J. Biol. Chem.* **1990**, *265*, 22348−22357.
(3) Kamigaichi, T.; Nakashima, M.; Tani, H. Japanese patent JP 11158109 A2 1999 [CAN 131:72775 AN 1999: 378444.
(4) Wilson, K. E.; Tsou, N. N.; Guan, Z.; Ruby, C. L.; Pelaez, F.; Gorrochategui, J.; Vicente, F.; Onishi, H. R. *Tetrahedron Lett.* **2000**, *41*, 8705−8709.

10.1021/ja0509984 CCC: $30.25

Scheme 1. Dynamic Isomerism Exhibited by Coleophomone D (**4a**−**d**)



the sake of clarity, we would later baptize the two unnamed Shionogi compounds **3** and **4**, coleophomones C and D, respectively.

Our interest was sparked in the coleophomone family of compounds by a number of captivating features that they possessed. First, the extremely compact and condensed nature of the carbon framework, consisting of multiple interconnected ring systems, gifted the coleophomones with many synthetic challenges. The strain of an 11-membered macrocycle, exacerbated by the presence of 6 sp^2 carbon atoms, an ethereal oxygen, a fused aromatic ring, and a bridging six-membered carbocycle complete with a quaternary center, as found in coleophomones A−C (**1**−**3**), posed a particularly strenuous synthetic obstacle. Continuing with the synthetic theme, coleophomones B (**2**), C (**3**), and D (**4**) also all bear a truculent tricarbonyl unit with a highly labile central proton (C-9). In coleophomone A (**1**), this tricarbonyl unit has been fused to the proximal aldehyde present in its precursor, coleophomone B (**2**), by means of an aldol reaction, thus forming a delicate spirocycle which endows coleophomone A (**1**) with yet higher degrees of tension and strain in comparison to its siblings. Despite this added strain, the Merck paper suggested that coleophomones A (**1**) and B (**2**) could be interconverted at will, an observation that was set to become pivotal to our investigations.[4] The final thread to our developing interest in the coleophomone family arose from the structural incongruity so blatantly exhibited by coleophomone D (**4**). In this interesting compound, which also lacks the molecular tie-up of a macrocycle, the substitution pattern on the aromatic ring (at C-2 and C-7) has been switched from that present in all its other siblings. This feature seemed to be at odds with all of the obvious theories about the biogenesis of the coleophomone family.[5] Furthermore, coleophomone D (**4**), as mentioned above, exists as a complex mixture of isomers making spectral investigation and elucidation somewhat complicated; indeed, coleophomone D's structure had originally been assigned on the basis of information garnered from synthetic derivatives not from the compound itself.[3] We felt that a laboratory synthesis of coleophomone D (**4**) might

(5) Bode, J. W.; Suzuki, K. *Tetrahedron Lett.* **2003**, *44*, 3559−3563.

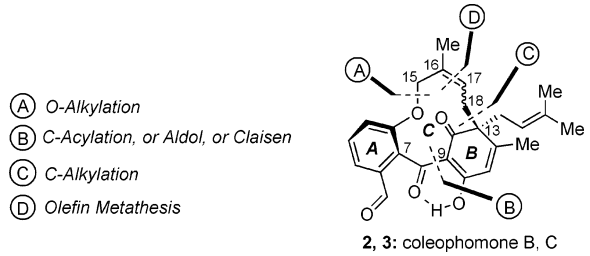


Figure 2. Retrosynthetic analysis for coleophomones B (**2**) and C (**3**). Strategies A−D.

go a long way toward unraveling these apparently confusing issues by confirming coleophomone D's unusual substitution pattern and by facilitating investigation into its unique structural features. Thus, we set forth on a program aimed at achieving the total syntheses of all of the known members of the coleophomone class. Our successful accomplishment of this goal for coleophomones B−D (**2**−**4**),[6,7] using newly developed acyl cyanide coupling technologies and a pleasing olefin metathesis reaction, is related herein.

Retrosynthetic Analysis and the Development of a Blueprint for the Total Synthesis

Our first observation, when considering how to approach the synthesis of this class of compounds, was that the 11-membered macrocycle of the coleophomones A−C (**1**−**3**) should be seen as the critical feature, for it undoubtedly presented the most challenging test for our synthetic acumen. For reasons already delineated above, this unusual ring is highly strained and compacted, and, as such, it could be anticipated that it would show some reluctance to snap shut. A particularly powerful ring closing reaction would, therefore, need to be found capable of rising to such a formidable challenge. Because it had been reported that coleophomones A (**1**) and B (**2**) could be interconverted at will,[4] it did not matter which of these two compounds we targeted initially; however, we did hope to hit upon a macrocycle closure strategy that would allow us relatively easy access to both geometric isomers of the macrocyclic $\Delta^{16,17}$ double bond,[8] for therein lay the only difference between the two targets, coleophomones B (**2**) and C (**3**). Independent of our choice of position at which to attempt macrocycle closure, a decision that would change over the course of the investigation according to developing circumstances, three pivotal disconnections were identified, which severed the molecule into three key fragments. These disconnections, not the subject of change, except in their order of execution, as the macrocycle closure strategy evolved, were O-alkylation, C-acylation, and C-alkylation (disconnections A−C, respectively, Figure 2). Finally, from our initial cursory survey, we surmised that any technologies developed to unite these fragments in the forward sense when targeting coleophomones A−C (**1**−**3**) could be concomitantly applied to the rapid assembly of coleophomone D (**4**), albeit after simple alterations in the substitution pattern of the aromatic ring portion.

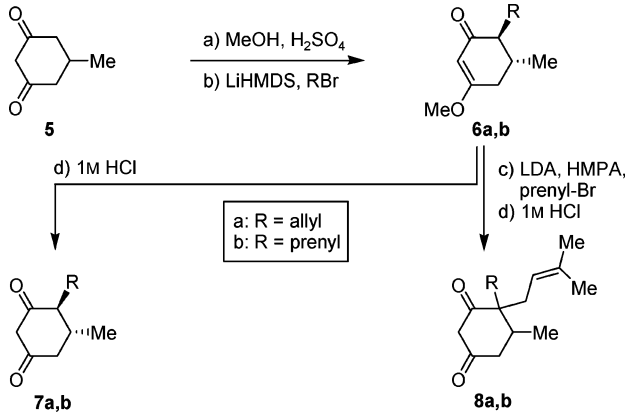
(6) Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276−3281.
(7) Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G. *Chem. Commun.* **2002**, 2478−2479.
(8) For clarity, we have opted to use the same numbering system for the coleophomones and their precursors, throughout this paper, as was used in the last isolation paper (ref 4).

Our first in-depth proposal involved disconnection of the macrocycle at the ethereal linkage (Figure 2, first generation approach: macrocycle formation using O-alkylation − disconnection A). This scission offered the possibility of closing the macrocycle either by using a traditional alkylation reaction, wherein a phenoxide nucleophile would attack an electrophilic allylic halide thereby forming the requisite new carbon−oxygen bond, or by a newer Tsuji−Trost-type reaction (already applied to similar macrocyclization tasks)[9] between the previously envisioned phenoxide, and, in this instance, an allyl carbonate-derived palladium π-allyl complex as electrophile. We envisioned that a second alkylation at C-13 (Figure 2, disconnection C), to precede this ring closure, was also feasible and would allow us a facile means to vary the C-15 to C-18 unit of the molecule and, hence, access both coleophomones A/B (**1**/**2**) and C (**3**). However, to successfully employ this strategy, the means to construct the two requisite variations of the 1,2,3-trisubstituted aromatic ring (one for coleophomones A−C (**1**−**3**) and one for coleophomone D (**4**)), the highly unsaturated six-membered ring, and the tricarbonyl structural motif centered around C-9 would have to be found. It was at the latter of these additional synthetic hurdles (Figure 2, disconnection B) that this first generation approach fell, but not before synthesis of some 1,3-cyclohexadiones, also suitable for use in our forthcoming forays, had been accomplished and optimized.

In moving on to the next generation approach, we upgraded the problem of how to assemble the recalcitrant tricarbonyl moiety to a priority slot. We considered that this key C-acylation reaction (indicated as disconnection B) might benefit from being intramolecular rather than intermolecular. Thus, we were prompted to investigate whether this reaction could be used to close the macrocycle itself (Figure 2, second generation approach: macrocycle formation using C-acylation − disconnection B). However, this approach was also set to flounder as the C-acylation continued to prove its intransigence. However, as of yet unsuccessful in reaching our goal, our investigations had allowed us to garner much useful reconnaissance information, which we judiciously applied to the charting of our next route forward. In our continuing search for viable C-acylation methods, we had come across several crucial leads in the literature, discussed in detail later in the text. Ideas from these studies, published by a number of different groups, led us to eventually discover and develop the reaction in which aromatic acyl cyanides could be united with a suitable 1,3-cyclohexadione. Unfortunately, however, when attempted intramolecularly, as a way of closing the macrocycle, this method proved not to have the required brawn and, thus, also failed to close the macrocycle.

Hence, it was with that failure that we moved on to the third generation approach to the macrocycle closure (Figure 2, third generation approach: macrocycle formation using C-alkylation − disconnection C), having already solved two important problems, first, how to synthesize an appropriate 1,3-cyclohexadione, and, second, how to unite it with a suitable 1,2,3-substituted aromatic unit to form the coleophomone's tricarbonyl motif. Unfortunately, macrocycle closure by alkylation at C-13 would also soon prove to be a dead-end, as, once again, the proposed ring-closure reaction was incapable of meeting the onerous criteria. This strategy was, therefore, quickly consigned to history's discard pile alongside its two unsuccessful predecessors.

Scheme 2. Synthesis of Mono- and Disubstituted 1,3-Cyclohexadiones **7a**,**b** and **8a**,**b**[a]



[a] Reagents and conditions: (a) concentrated H_2SO_4 (cat.), MeOH, 65 °C, 12 h, 85%; (b) LiHMDS (1.05 equiv), THF, −78 °C, 1 h; then allyl- or prenyl-Br (1.1 equiv), −78 to 0 °C, 3 h, 80−85%; (c) LDA (1.1 equiv), THF, slow addition of a solution of **6a** or **6b** in THF:HMPA (7:1), −78 °C, 1 h; then prenyl-Br (2.0 equiv), −78 to 20 °C, 12 h, 89%; (d) 1 M HCl:THF (1:10), 25 °C, 14 h, 95−98%. LiHMDS = lithium bis(trimethylsilyl)amide; LDA = lithium diisopropylamide; HMPA = hexamethylphosphoramide.

By now, we understood better than ever that the coleophomone macrocycle's closure demanded a special type of reaction with the power to bind together two reluctant partners to make a highly congested and strained ring. It was from this context that our fourth and final retrosynthetic strategy emerged (Figure 2, fourth generation approach: macrocycle formation using olefin metathesis − disconnection D). In this retrosynthetic blueprint, we proposed severing the macrocyclic $\Delta^{16,17}$ double bond in the hope that the forward reaction using olefin metathesis might constitute the auspicious macrocycle closing procedure that had been so elusive thus far. Retrosynthetically, after this disconnection was made, we stuck to familiar territory by proposing disconnections A−C (Figure 2) to break the molecule down into more digestible portions. Upon its application, this design came to fruition, having at its climax an amazing sequence of reactions, led by a powerful olefin metathesis reaction, which was able to supply both coleophomones B and C from a single common precursor. Before we unravel the intricate secrets of this conquest, which leaves the olefin metathesis reaction with a sterling set of credentials, we shall detail the important lessons learned, and technologies developed, from the earlier strategies that ended prematurely without the hope for success.

The Total Synthesis of Coleophomones B (2) and C (3)

First Generation Strategy: Attempted Macrocycle Formation Using O-Alkylation and Attempted Synthesis of Coleophomone D (4). Our first, and relatively simple, task was to find a means of synthesizing the requisite 1,3-cyclohexadiones (**8**) that had been envisioned as key fragments for the synthesis of the coleophomones A−D (**1**−**4**). This assignment was successfully accomplished using the short synthetic sequence shown in Scheme 2. Thus, the commercially available, C_s-symmetrical 5-methyl-1,3-cyclohexadione (**5**) was desymmetrized upon its protection as the corresponding methyl vinylogous ester. The vinylogous ester formation was bought about

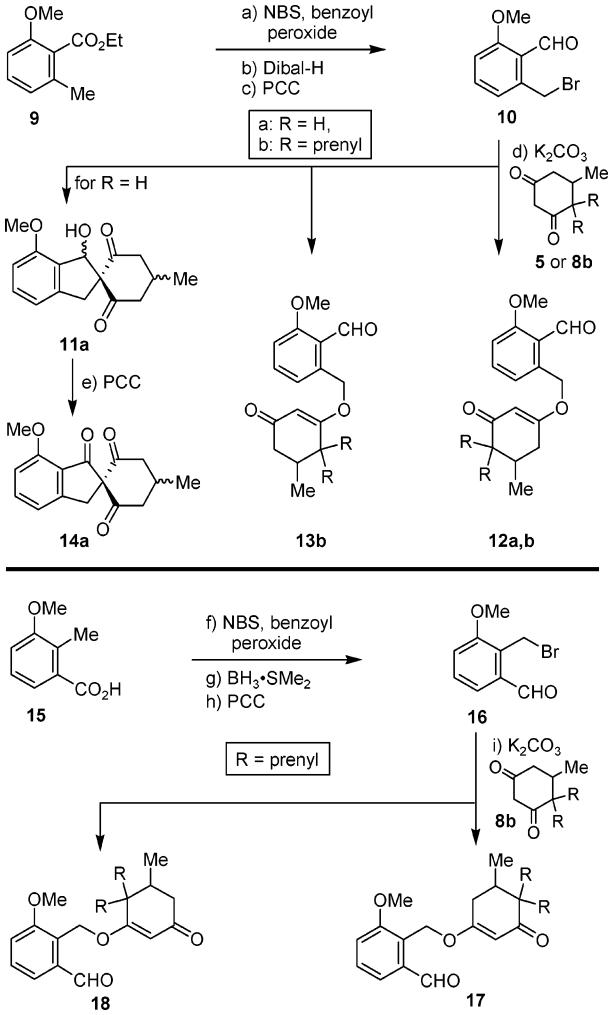
(9) Wei, Q.; Harran, S.; Harran, P. G. *Tetrahedron* **2003**, *59*, 8947−8954.

by refluxing 1,3-cyclohexadione **5** in methanol with catalytic amounts of concentrated H_2SO_4, in a protocol taken directly from the literature.[10] Alkylation adjacent to the carbonyl group was then readily achieved by means of a LiHMDS-induced enolate formation, followed by a quench with prenyl-Br (or allyl-Br), to afford **6a** or **b** in high yield (80−85%), and as 4:1 mixture of trans:cis isomers. The second alkylation proved to be much less trivial to achieve. Actualization of the desired transformation required the careful maintenance of a set of rigorously derived reaction conditions before the pertinent bisalkylated congener could be attained. It required that LDA be used to form the enolate by very slow addition of a solution of **6** in THF:HMPA (7:1) to the preformed base; this part of the procedure was then followed by the slow addition of excess prenyl-Br to the newly formed enolate, and, finally, the reaction mixture was left to warm from −78 to 20 °C over the course of a 12 h period. When this protocol was stringently adhered to, the bisalkylated congeners could be attained in high yield (89%). Deprotection of the methyl vinylogous ester to finally reveal the 1,3-cyclohexadiones **8a** or **8b** was accomplished in high yield (95−98%) using 1 M HCl in THF at ambient temperature. This reliable and concise sequence of reactions would be used in all subsequent synthetic forays. For the time being, however, the focus of our attention shifted to the investigation of how **8b** might be attached to a suitable 1,2,3-trisubstituted aromatic unit to gain rapid access to the simplest (i.e., bearing no macrocycle) target, coleophomone D (**4**).

Commercially available 2-methoxy-6-methyl benzoic acid ethyl ester (**9**) was chosen as a potentially apt starting point for the construction of all of the aromatic fragments required for the synthesis of each of the various coleophomones (Scheme 3). Initially, as part of our efforts toward the synthesis of coleophomone D (**4**), ester **9** was first brominated at its free benzylic position (NBS, benzoyl peroxide, CCl_4) in high yield (98%) and then reduced to the corresponding aldehyde (**10**) using a two-step reduction-partial reoxidation sequence (Dibal-H, followed by PCC; in yields of 93% and 78%, respectively). C-Alkylation of the 1,3-cyclohexadione **8b** with this newly made benzylic bromide (**10**) was then attempted using K_2CO_3 as base. Unfortunately, the only products isolated from this reaction were those obtained through O-alkylation of the 1,3-cyclohexadione **8b** by **10**. Both of the possible regioisomers, **12b** and **13b**, were attained in yields of 55% and 19%, respectively. Variation of the base or the use of additives, such as a crown ether (15-crown-5), failed to divert this reaction from its disappointing course. The same reaction, attempted using the unsubstituted 1,3-cyclohexadione **5** instead of **8b**, still afforded mostly the product of O-alkylation, **12a** (61%); however, on this occasion a small amount of the desired C-alkylation product, **11a** (1.5:1 inseparable mixture of stereoisomers, 22%), was also recovered from the reaction mixture. It should be noted that **11a** was isolated and existed entirely in the closed spirocyclic form, reminiscent of coleophomone A (**1**), rather than as the open chain aldehyde/1,3-dione arrangement, which shares more similarities with coleophomones B and C (**2** and **3**). Neither changes to the base employed, nor the addition of 15-crown-5, altered the distribution of products for this reaction. In an attempt to investigate the possibility of building up the carbon framework of coleophomones A−C (**1**−**3**) from the spirocycle **11a**, the benzylic alcohol of **11a** was oxidized using PCC to furnish the spirocycle **14a** (inseparable mixture of stereoisomers 1.5:1, 65%). However, this problematic avenue to our investigations was finally abandoned when all attempts (using IBX,[11] or the Saegusa method[12]) to introduce the requisite α,β-unsaturation to the six-membered ring failed.

Switching the substituent's position on the aromatic ring (i.e., using benzylic bromide **16**, obtained from commercially available **15** by a series of standard reactions, rather than its analogue

Scheme 3. Abortive Atempts To Construct the Precursors for the First Generation Approach to the Macrocycle-Bearing Coleophomones A−C (**1**−**3**) and for the Synthesis of Coleophomone D Using the Regioisomeric Compounds **10** and **16**: O- versus C-Alkylation[a]



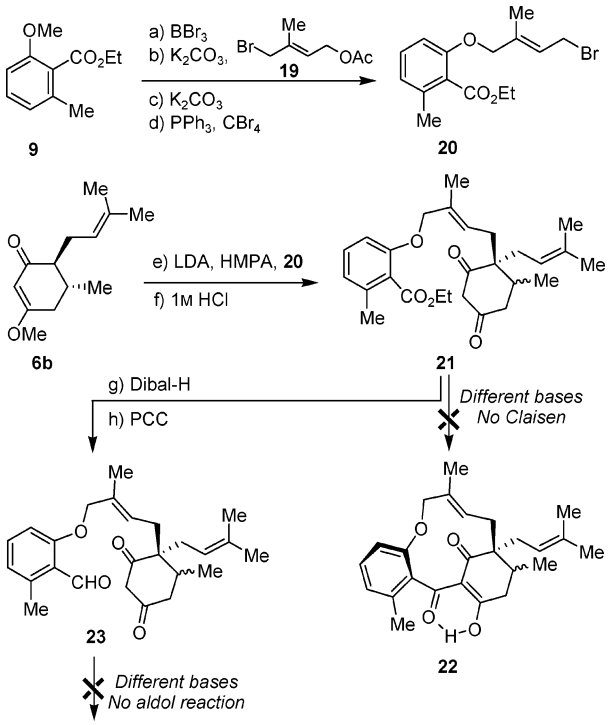
[a] Reagents and conditions: (a) NBS (1.1 equiv), benzoyl peroxide (0.1 equiv), CCl_4, 77 °C, 3 h, 98%; (b) Dibal-H (2.5 equiv), toluene, −78 to 25 °C, 2 h, 93%; (c) PCC (1.5 equiv), CH_2Cl_2, 25 °C, 3.5 h, 78%; (d) **5** or **8b** (1.0 equiv), K_2CO_3 (2.0 equiv), acetone, 25 °C, 0.5 h; then **10** (1.0 equiv), 56 °C, 0.5 h, 61% **12a** plus 22% **11a** for R = H; 55% of **12b** plus 19% of **13b** for R = prenyl; (e) PCC (3.0 equiv), CH_2Cl_2, 25 °C, 3 h, 65%; (f) NBS (1.0 equiv), benzoyl peroxide (0.1 equiv), CCl_4, 77 °C, 5 h, 97%; (g) BH_3•SMe_2 (2.0 equiv), THF, 25 °C, 12 h, 91%; (h) PCC (1.5 equiv), CH_2Cl_2, 25 °C, 2 h, 71%; (i) **8b** (1.0 equiv), K_2CO_3 (2.0 equiv), acetone, 25 °C, 0.5 h; then **16** (1.0 equiv), 56 °C, 0.5 h, 67% **17** plus 15% **18**. NBS = *N*-bromosuccinimide; Dibal-H = diisobutylaluminum hydride; PCC = pyridinium chlorochromate.

(10) Constantino, M. G.; Beltrame, M., Jr.; Faria de Medeiros, E.; Jose da Silva, G.-V. *Synth. Commun.* **1992**, *19*, 2859−2864.

(11) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996−1000.

(12) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.

Scheme 4. Second Generation Approach: Abortive Attempts for Intramolecular Claisen and Aldol Reactions[a]



[a] Reagents and conditions: (a) BBr_3 (2.4 equiv), CH_2Cl_2, −78 °C, 0.5 h, 99%; (b) K_2CO_3 (3.0 equiv), **19** (1.5 equiv), acetone, 56 °C, 14 h, 84%; (c) K_2CO_3 (1.0 equiv), MeOH:H_2O (4:1), 25 °C, 20 min, 98%; (d) PPh_3 (2.4 equiv), CBr_4 (2.4 equiv), CH_3CN, 0 to 25 °C, 2 h, 86%; (e) LDA (1.2 equiv), THF, slow addition of a solution of **6b** in THF:HMPA (7:1), −78 °C, 1 h; then **20** (1.2 equiv), −78 to 20 °C, 12 h, 60%; (f) 1 M HCl:THF (1:10), 25 °C, 14 h, 92%; (g) Dibal-H (2.5 equiv), toluene, −78 to 25 °C, 2 h, 53% plus 30% reduction of 1,3-cyclohexadione moiety; (h) PCC (2.0 equiv), CH_2Cl_2, 25 °C, 2 h, 67%.

10) had no effect on the outcome of the alkylation reaction (**16** + **8b** → **17** and **18**, Scheme 3). Once again, only the undesired O-alkylation was observed with no significant change in the regiochemical outcome occurring either [**17** (67%) and **18** (15%)]. Thus, we were forced to rethink our strategy, casting the net wider in search of new technologies capable of uniting an appropriate aromatic fragment to a suitable 1,3-cyclohexadione to progress with our syntheses of the various coleophomones A−D (**1**−**4**).

Second Generation Strategy: Model Studies and Attempts at Macrocycle Formation Using Claisen, Aldol, or C-Acylation Reactions. Because C-acylation of a suitable 1,3-cyclohexadione represented the transformation that would give rise to products most closely resembling the target structures, we chose to move away from C-alkylation and focus on the feasibility of this reaction instead. To test this updated strategy, a means of rapidly accessing compounds such as **21** and **23** had to be found (Scheme 4). To this end, **9** was demethylated to reveal the free phenol in high yield (99%) using boron tribromide at −78 °C. The phenol was then alkylated with the known allylic bromoacetate **19**,[13] using potassium carbonate as base, in good yield (84%). Acetate deprotection, mediated by methanolic potassium carbonate, followed by conversion of the resultant allylic alcohol to its corresponding bromide using the PPh_3/CBr_4 complex, afforded key bromide **20** (84%, two steps).

(13) (a) Babler, J. H.; Buttner, W. J. *Tetrahedron Lett.* **1976**, *4*, 239−242. (b) Van Nguyen, T.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7969−7973.

The difficult alkylation, uniting the previously synthesized vinylogous ester **6b** with this newly made bromide **20**, was then realized in 60% yield using the conditions (LDA/HMPA) that had been so stringently derived at the beginning of our investigations (vide supra). Hydrolysis of the vinylogous ester moiety using 1 M HCl afforded **21** (as a 1.5:1 mixture of stereoisomers) in high yield (92%). With the key intermediate **21** now synthesized, it was time to attempt the C-8/C-9 bond formation using an intramolecular Claisen-type condensation. Unfortunately, no conditions could be found to encourage the desired merger, despite a wide ranging trawl through the possible base options (K_2CO_3, Et_3N, LiHMDS) and extensive experimentation with other reaction variables (e.g., temperature, solvent, concentration). To investigate whether an aldol reaction might prove to be a better way of forming the requisite carbon−carbon bond, the ester **21** was reduced using Dibal-H. This reduction was plagued by the concomitant reduction of the 1,3-cyclohexadione, but the situation was made even worse if the preceding vinylogous ester was used instead of its deprotected congener **21**. The desired benzylic alcohol could be attained (albeit in a modest yield of 53%) and oxidized to aldehyde **23** in preparation for the aldol reaction attempts. Unfortunately, the desired aldol macrocyclization could not be accomplished either.

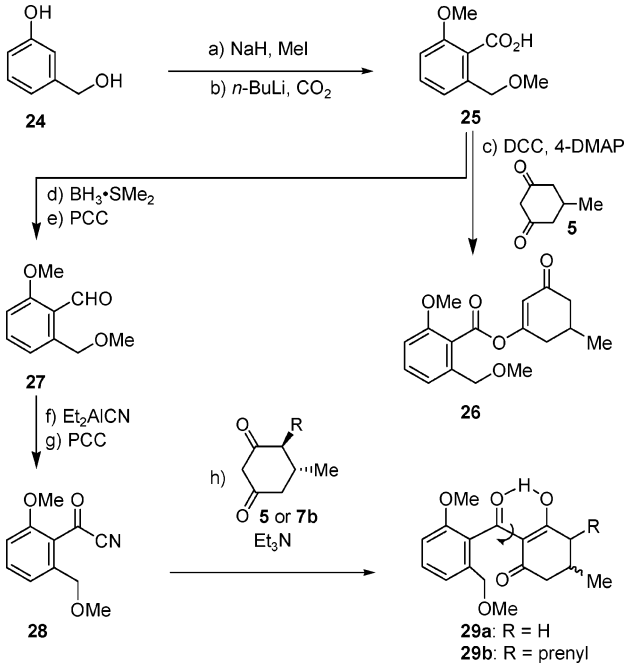
Given the poor results obtained from our studies thus far, we knew that our next plan had to offer convincing improvements in circumstances if we were to hit upon a suitable reaction for forming the carbon−carbon bond between C-8 and C-9 of the coleophomone skeleton, rather than simply making more unwanted O-alkylated/acylated analogues of the 1,3-dione.

After a comprehensive survey of the literature looking into known methods for acylation of 1,3-dicarbonyls, we uncovered a series of interesting precedents.[14−19] The vast majority of existing examples for the C-acylation of a 1,3-dicarbonyl involved initial O-acylation followed by a catalyzed (mediated by heat, Lewis acid, or 4-DMAP) rearrangement to the C-acylated congener. Where one, or both, of the 1,3-dicarbonyl's functionalities was an ester, the rearrangement was relatively trivial to accomplish.[14,15,18] However, where both of the carbonyls were ketones, the rearrangement was far from facile.[16−19]

Due to the ease with which we could prepare the requisite benzoic acid precursor **25**[20] (Scheme 5), we chose to start our own model studies using a 1993 protocol[18] in which a carboxylic acid could be coupled to a 1,3-dicarbonyl system using DCC and 4-DMAP. This reaction was reported to furnish the O-acylated product initially, but upon elevation of the reaction temperature this intermediate could be coaxed into rearranging to its C-acylated isomer. Unfortunately, when these conditions were applied to **25**, no such rearrangement of the initially formed O-acylated benzoic acid **26** was observed; most likely, this failure was due to severe steric hindrance arising from the presence of two *ortho*-substituents on the aromatic ring.

(14) (a) Ukita, T.; Nojima, S.; Matsumoto, M. *J. Am. Chem. Soc.* **1950**, *72*, 5143−5144. (b) Rogers, N. A. J.; Smith, H. *J. Chem. Soc.* **1955**, 341−346.
(15) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087−2088.
(16) Akhrem, A. A.; Lakhvich, F. A.; Budai, S. I.; Khlebnicova, T. S.; Petrusevich, I. I. *Synthesis* **1978**, 925−927.
(17) Oliver, J. E.; Lusby, W. R. *Tetrahedron* **1988**, *44*, 1591−1596.
(18) Tabuchi, H.; Hamamoto, T.; Ichihara, A. *Synlett* **1993**, 651−652.
(19) Ali, A. S.; Liepa, A. J.; Thomas, M. D.; Wilkie, J. S.; Winzenberg, K. N. *Aust. J. Chem.* **1994**, *47*, 1205−1210.
(20) Coutts, S. J.; Wallace, T. W. *Tetrahedron* **1994**, *50*, 11755−11780.

Scheme 5. Second Generation Approach: Chemoselective C- versus O-Acylation of 1,3-Cyclohexadiones Using Acyl Cyanides as Acylating Agents[a]



[a] Reagents and conditions: (a) NaH (4.0 equiv), MeI (6.0 equiv), THF, 1 h at 25 °C plus 2 h at 67 °C, 98%; (b) see ref 18; (c) **5** (1.0 equiv), DCC (1.1 equiv), 4-DMAP (0.1 equiv), toluene, 110 °C, 72 h, 43%; (d) BH_3•SMe_2 (2.2 equiv), THF, 25 °C, 15 h, 98%; (e) PCC (1.5 equiv), CH_2Cl_2, 25 °C, 2 h, 78%; (f) Et_2AlCN (2.0 equiv), toluene, 0 °C, 1 h, 96%; (g) PCC (4.0 equiv), CH_2Cl_2, 40 °C, 12 h, 62%; (h) **5** or **7b** (1.0 equiv), Et_3N (1.5 equiv), THF, 25 °C, 12 h, 84% of **29a** and 71% of **29b**. DCC = 1,3-dicyclohexylcarbodiimide; 4-DMAP = 4-(dimethylamino)pyridine.

It had been known for some time that cyanide ions are catalysts able to facilitate the rearrangement of O-acylated 1,3-diones to furnish their C-acylated variants[21,22] via the intermediacy of an acyl cyanide. More recently, a report appeared in which acyl cyanides had been employed directly to C-acylate 1,3-dicarbonyl compounds under mild conditions.[23] No O-acylation was detected when this protocol, using triethylamine as base, was employed. Attracted by the mild conditions of this transformation, we wanted to test its scope within systems useful to our synthesis of the coleophomones. Thus, benzoic acid **25**[20] was reduced to the corresponding aldehyde **27** using a two-step reduction-partial reoxidation procedure employing BH_3•SMe_2 and PCC (overall yield 76%, Scheme 5). The resulting aldehyde **27** was reacted with Nagata's reagent (Et_2AlCN) to afford the cyanohydrin, which could then be oxidized to the acyl cyanide **28** using PCC (60%, two steps).

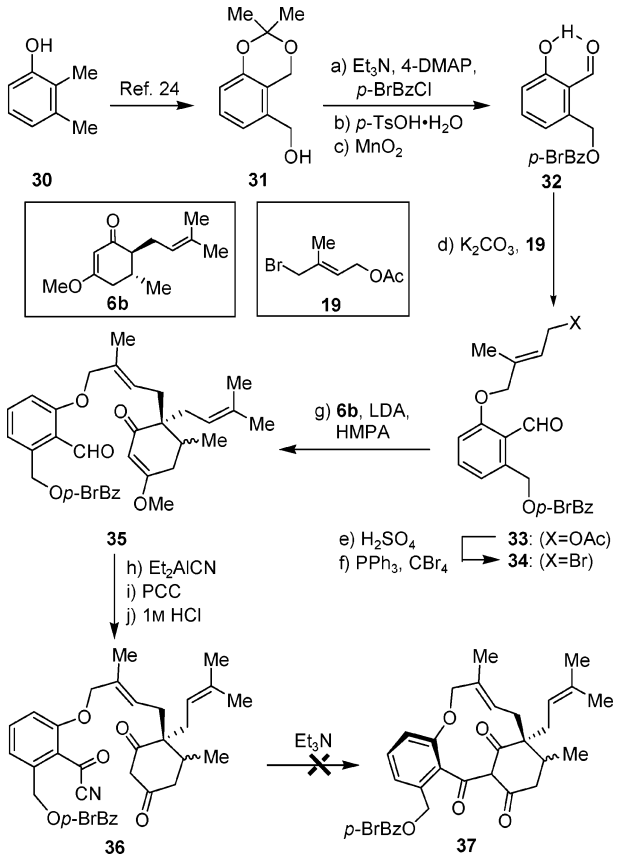
With the acyl cyanide **28** now in hand, we began to examine its reaction with some of the 1,3-cyclohexadiones that we had synthesized previously. In the presence of triethylamine, acyl cyanide **28** reacted smoothly with both 1,3-cyclohexadiones **5** and **7b** (furnishing **29a** or **29b** in yields of 84% and 71%, respectively, Scheme 5). The adduct **29b** arising from the reaction between **28** and **7b** was formed as a mixture of four isomers, two stereo- and two atropisomers (6:4:4:1). To our dismay, however, no reaction was observed with the disubstituted 1,3-cyclohexadione **8b**, under the established conditions, and, furthermore, if the temperature was elevated in an attempt to coax the reluctant partners into union, only decomposition of the acyl cyanide **28** was observed. It was therefore clear that the two partners most relevant to a synthesis of the coleophomones (**28** and **8b**) would stretch the scope of this reaction to its limits, if indeed, they could be encouraged to participate at all by further adaptation of the conditions. This recalcitrance was observed because one partner, **28**, was aromatic (and was thus deactivated) and had two *ortho*-substituents increasing steric hindrance in the reaction vicinity, and the other, **8b**, bore a proximal quaternary center that endowed it with similarly detrimental space constraints. In an attempt to tip the balance in our favor, we decided to investigate the intramolecular reaction of an appropriate acyl cyanide with a suitable 1,3-cyclohexadione rather than the intermolecular variant. Of course, this ambitious plan would also use the reaction to close the coleophomone macrocycle and, as such, would constitute a very elegant solution to the problem of how to construct this 11-membered ring. An added advantage to this approach was that, if successful, it would furnish an adduct that was only a few steps shy of coleophomone B (**2**).

To access the key acyl cyanide coupling compound **36**, commercially available phenol **30** was first transformed into the acetonide/primary alcohol **31** using a reaction sequence taken directly from the literature (Scheme 6).[24] The primary alcohol **31** was then protected as its *para*-bromobenzoate ester, this protecting group having been chosen because it offered the best possibility for obtaining crystalline intermediates, suitable for X-ray analysis, later on in the synthesis. Acetal deprotection using *p*-TsOH, followed by MnO_2-mediated benzylic oxidation, gave the phenolic aldehyde **32** (72%, three steps). Phenol **32** was then alkylated with bromoacetate **19**[13] to furnish the acetate **33** in good yield (74%). The acetate functionality of **33** was then deprotected under acidic conditions (cat. H_2SO_4), and the resultant primary allylic alcohol was converted to bromide **34** using the PPh_3/CBr_4 complex (53%, two steps). Bromide **34** was then employed as the alkylating agent for reaction with the LDA-derived enolate of vinylogous ester **6b**, to furnish the crucial intermediate **35** in 64% yield and as a 1.6:1 mixture of stereoisomers. The benzylic aldehyde group of **35** was then transformed to the corresponding acyl cyanide moiety using the conditions we had developed previously (60%, two steps). After deprotection of the vinylogous ester (1 M HCl), the synthesis of the pivotal acyl cyanide coupling substrate **36** (as a 1.5:1 mixture of stereoisomers) had been completed. However, the macrocyclization coupling reaction did not work (**36**→**37**) under any of the conditions we tested (variable temperature, solvent, etc.).

Our newly developed acyl cyanide coupling reaction had, at last, shown us an attractive way to make the fragile tricarbonyl unit of the coleophomones; however, we had also discovered that, as it stood, it had limits that prevented its use in our desired scenarios. It could only be employed with a carefully selected pair of less sterically encumbered substrates. Therefore, on the basis of our initial model studies, we rationalized that using 1,3-cyclohexadione **7b** (bearing no quaternary center) we could succeed in the coupling reaction even with a suitable, but hindered, 1,2,3-substituted aromatic fragment. Successful ac-

(21) Oliver, J. E.; Wilzer, K. R.; Waters, R. M. *Synthesis* **1990**, 1117−1119.
(22) Flores Montes, I.; Burger, U. *Tetrahedron Lett.* **1996**, *37*, 1007−1010.
(23) Tang, Q.; Sen, S. E. *Tetrahedron Lett.* **1998**, *39*, 2249−2252.
(24) Suzuki, M.; Sugiyama, T.; Watanabe, M.; Murayama, T.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51*, 1121−1127.

Scheme 6. Second Generation Approach: Attempts at Intramolecular C-Acylation of the 1,3-Cyclohexadione Moiety Using an Acyl Cyanide as the Coupling Partner[a]

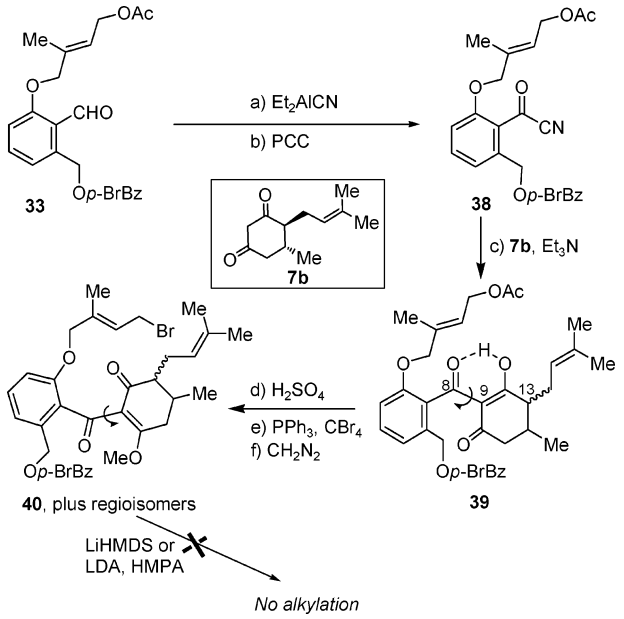


[a] Reagents and conditions: (a) Et_3N (1.5 equiv), *p*-BrBzCl (1.05 equiv), 4-DMAP (0.05 equiv), CH_2Cl_2, 25 °C, 20 min, 97%; (b) *p*-TsOH·H_2O (0.3 equiv), THF:H_2O (3:2), 75 °C, 10 h, 85%; (c) MnO_2 (10 equiv), EtOAc, 25 °C, 1.5 h, 87%; (d) K_2CO_3 (2.0 equiv), **19** (1.5 equiv), acetone, 56 °C, 2 h, 74%; (e) H_2SO_4 (cat.), MeOH, 25 °C, 10 h, 72%; (f) PPh_3 (2.0 equiv), CBr_4 (2.0 equiv), CH_3CN, 0 to 25 °C, 1.5 h, 73%; (g) LDA (1.2 equiv), THF, slow addition of a solution of **6b** in THF:HMPA (7:1), −78 °C, 0.5 h; then **34** (1.2 equiv), −78 to 20 °C, 12 h, 64%; (h) Et_2AlCN (1.1 equiv), toluene, 0 °C, 1 h, 96%; (i) PCC (4.0 equiv), CH_2Cl_2, 40 °C, 10 h, 62%; (j) 1 M HCl:THF (1:10), 25 °C, 18 h, 83%. *p*-BrBzCl = 4-bromobenzoyl chloride; *p*-TsOH = *p*-toluenesulfonic acid.

complishment of this task would then leave us only the hurdle of creating the quaternary center in a macrocyclization step. Thus, it was that the key concepts of our third generation approach were born.

Third Generation Strategy: Attempted Macrocycle Formation Using C-Alkylation at C-13. Having previously synthesized aldehyde **33**, it was convenient to begin our third synthetic foray with this advanced intermediate. The aldehyde **33** was converted to the corresponding acyl cyanide **38** (Scheme 7) using our established set of conditions (60%, two steps). As we had predicted, this compound could then be successfully coupled to 1,3-cyclohexadione **7b** at ambient temperature, furnishing **39** (as a mixture of two stereoisomers each of which existed as two atropisomers) in a good yield (76%). Satisfied by the fact that our molecule was smoothly and rapidly gaining in its resemblance to the targeted coleophomone skeleton with each new step chartered, we set about converting the acetate to the corresponding bromide, as was required for the key macrocyclization-alkylation event. Acidic conditions (cat. H_2SO_4) were employed to hydrolyze the acetate (74%). It should

Scheme 7. Third Generation Approach: Attempts at an Intramolecular Alkylation[a]

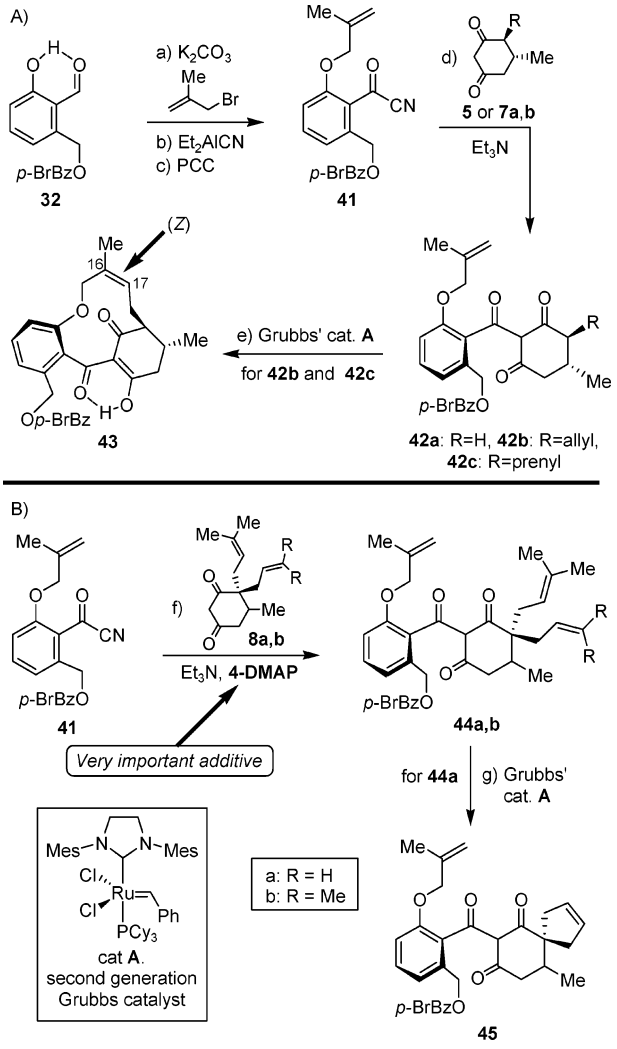


[a] Reagents and conditions: (a) Et_2AlCN (1.5 equiv), toluene, 0 to 25 °C, 1 h, 97%; (b) PCC (4.0 equiv), CH_2Cl_2, 40 °C, 10 h, 62%; (c) **7b** (1.0 equiv), Et_3N (2.0 equiv), THF, 25 °C, 12 h, 76%; (d) H_2SO_4 (cat.), MeOH, 25 °C, 10 h, 74%; (e) PPh_3 (1.5 equiv), CBr_4 (1.5 equiv), CH_3CN, 0 to 25 °C, 3 h, 90%; (f) excess of CH_2N_2, Et_2O, 0 °C, 0.5 h, 78%.

be noted here that the standard basic conditions for acetate hydrolysis were rejected due to the strong acidity, and, thus lability, of the tricarbonyl C-9 proton. Upon treatment of any analogue bearing this tricarbonyl unit with even mild base, a water-soluble salt was formed, manipulation became fraught with problems, and TLC analysis was rendered almost useless unless each sample was acidified prior to spotting, and, even then, streaking plagued the procedure. After the acetate deprotection, the resultant primary allylic alcohol was transformed to the bromide using the PPh_3/CBr_4 complex (90%). In preparation for the pivotal alkylation step, the tricarbonyl group was then protected by converting it into a mixture of all its possible regioisomeric methyl vinylogous esters. This protection reaction affording allylic bromide **40** in high yield (overall 78%, Scheme 7), as a complex mixture of stereo- and atropisomers (as well as the aforementioned regioisomers) was facilitated by diazomethane as the methylating agent. Disappointingly, the macrocyclization-alkylation reaction failed, even under the specially devised conditions that had previously been so successful in generating this quaternary center in analogous compounds. At this stage, we needed no further evidence that closure of the coleophomone macrocycle was extremely intransigent and hard to accomplish; an entirely new approach was needed for this key bond-forming reaction.

Fourth Generation Strategy: Model Studies and the Successful Syntheses of Coleophomones B (2) and C (3) Using Olefin Metathesis To Form the Macrocycle. Due to the acute awareness we had now developed of the challenges involved in forming the coleophomone macrocycle, we decided that proof of principle must be obtained for our new olefin metathesis macrocyclization strategy, alongside the answers to many probing questions relating to the scope of such a metathesis reaction, before we expended too much energy on the synthesis of key precursors to the real target systems. The

Scheme 8. Fourth Generation Approach: (A) Stereospecific Formation of (*Z*)-11-Membered Macrocycle **43** via Olefin Metathesis; (B) 4-DMAP-Mediated Coupling of Acyl Cyanide **41** with Disubstituted 1,3-Cyclohexadiones **8a**,**b** and Olefin Metathesis of **44a**[a]



[a] Reagents and conditions: (a) K_2CO_3 (2.0 equiv), 3-bromo-2-methylpropene (1.5 equiv), acetone, 56 °C, 2 h, 91%; (b) Et_2AlCN (1.1 equiv), toluene, 0 to 25 °C, 1 h, 82%; (c) PCC (4.0 equiv), CH_2Cl_2, 40 °C, 12 h, 73%; (d) **5**, **7a**, or **7b** (1.2 equiv), Et_3N (2.0 equiv), THF, 25 °C, 6−12 h, 91−98%; (e) cat. **A** (0.2 equiv), CH_2Cl_2, 40 °C, 5 h, 60% for **42b**; cat. **A** (0.3 equiv), CH_2Cl_2, 40 °C, 18 h, 30% for **42c**; (f) **8a**,**b** (1.2 equiv), Et_3N (2.0 equiv), 4-DMAP (1.0 equiv), THF, 25 °C, 72−96 h, 83% of **44a** and 86% of **44b**; (g) cat. **A** (0.1 equiv), CH_2Cl_2, 40 °C, 1 h, 85%. Cy = cyclohexyl; Mes = mesityl.

challenges of constructing medium-sized rings by any method are well known; in rings having 10−12 members, strain and congestion can easily frustrate attempts at their formation, even with much simpler exemplars. Olefin metathesis had already proved its value in this arena, the synthesis of 11-membered rings, in just a few instances when our investigations were at the planning stages.[25] However, all of the literature examples involved situations distinctly simpler and more favorable than the coleophomone's difficult skeleton. We knew, therefore, that success, if it came to us, would require this reaction to be pushed far beyond its existing boundaries at the time.

Model Studies Undertaken To Validate the Olefin Metathesis Approach to Macrocylization. The first and most pressing query of the current investigation required us to examine whether olefin metathesis was capable of closing such a strained macrocycle in the first place. To resolve this issue, the model compound **42b** was synthesized as follows (Scheme 8A). The previously synthesized phenol **32** was alkylated with 3-bromo-2-methylpropene (K_2CO_3, refluxing acetone) in high yield (91%). The resulting aldehyde was converted into its acyl cyanide congener **41** using our established conditions (Nagata's reagent followed by PCC oxidation) in good yield (60%, two steps). The acyl cyanide **41** was then coupled with 1,3-cyclohexadione **7a**, in the presence of triethylamine, to afford the crucial metathesis precursor **42b** in high yield (91%). When **42b** was subjected to the first generation Grubbs catalyst[26] under its standard operating conditions, no macrocyclization was observed; fortunately for us, the second generation Grubbs catalyst (**A**)[27] triumphed where its predecessor had failed by succeeding in its task of inducing ring closure. Thus, when **42b** was treated with 20 mol % of Grubbs' catalyst **A**, in gently refluxing dichloromethane, for a period of 5 h, the macrocycle **43** was obtained in 60% yield as the sole product of the reaction. The newly formed macrocyclic double bond of **43** ($\Delta^{16,17}$ coleophomone numbering) was present exclusively in its *Z*-configuration. As a result of having incorporated the *para*-bromobenzoyl protecting group into our molecule, we were able to obtain a crystal of **43** that was suitable for X-ray analysis. This analysis[28] (see Figure 3) confirmed not only the molecule's complete structure, but also the macrocycle double bond geometry, and it revealed the arrangement of the enol within the tricarbonyl motif. Olefin metathesis had proved itself a viable ring-closing tool on a testing ground where so many other methods had already fallen foul of the devious coleophomone skeleton.

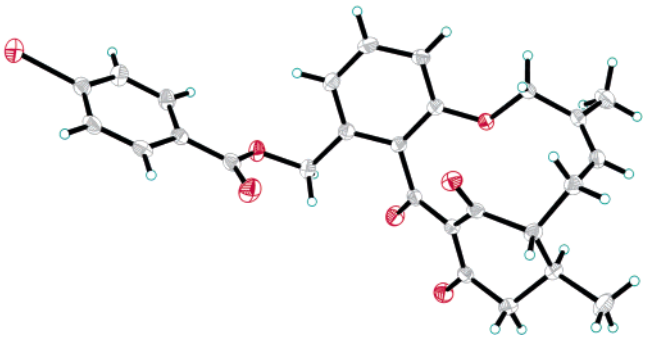


Figure 3. ORTEP representation of **43**.

(25) For selected examples of olefin metathesis being used to form 11-membered rings, see: (a) Wipf, P.; Stephenson, C. R. J.; Walczak, M. A. A. *Org. Lett.* **2004**, *6*, 3009−3012. (b) Ronsheim, M. D.; Zercher, C. K. *J. Org. Chem.* **2003**, *68*, 1878−1885. (c) Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1873−1876. (d) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429−1432. (e) Winkler, J. D.; Holland, J. M.; Kasparec, J.; Axelsen, P. H. *Tetrahedron* **1999**, *55*, 8199−8214. (f) El Sukkari, H.; Gesson, J.-P.; Renoux, B. *Tetrahedron Lett.* **1998**, *39*, 4043−4046. For insightful discussion, see also: (a) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061−7069. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.
(26) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.
(27) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(28) CCDC-187042 contains the supplementary crystallographic data for compound **43**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21 EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

This beautiful olefin metathesis macrocyclization was not the only pivotal victory that we were to notch up during this important phase of this adventure. Concomitantly, we had been continuing our search for acyl cyanide coupling reaction conditions that would allow for the participation of bisalkylated 1,3-cyclohexadiones in the union, and, not just, their monoalkylated analogues. We had already discovered that heat could not be of assistance, because elevated temperatures led to the decomposition of the acyl cyanide. We rationalized that the addition of the well-known acylation activator, 4-DMAP, might, however, provide the requisite mild assistance to cajole the two partners together. Sure enough, after some experimentation, we found that the addition of one equivalent of 4-DMAP to the reaction mixture facilitated the coupling of suitable hindered bis-*ortho*-substituted aromatic acyl cyanides with bisalkylated 1,3-cyclohexadiones, albeit after prolonged reaction times (72−96 h, Scheme 8B).

Armed with this vital new piece of knowledge, we set forth on our attempt to test the macrocyclization reaction on the simplest of the possible bisalkylated congeners, **44a** (Scheme 8B). This olefin metathesis precursor was the product of the coupling of acyl cyanide **41** and 1,3-cyclohexadione **8a**, a reaction that proceeded slowly, but with a remarkably high yield (83%) given the difficulty we had in defining reaction conditions that would work at all. Disappointingly, when **44a** was treated with Grubbs' catalyst **A** (10 mol %), in refluxing dichloromethane, for 1 h, the spirocycle **45** (Scheme 8b) was rapidly formed as the only product of the reaction (in 85% yield), in preference to the desired macrocycle. This latest result was quite interesting in itself, as this work[6] constituted a very early example of an olefin, which was geminally disubstituted at its terminus, participating in a metathesis cyclization reaction. Indeed, this reaction class remains exceptionally rare and is usually confined to the simplest substrates,[29] so to observe a prenyl group willingly participating in the metathesis reaction of such a complex substrate was truly a pleasing if not groundbreaking result.

Following the important discovery that a prenyl group could participate in a simple olefin metathesis cyclization event, we were anxious to see whether this new paradigm would stretch as far as a prenyl group also willingly engaging in the key and, much more challenging, macrocyclization reaction. We rationalized that if this approach was successful and could be employed, it might relocate the metathesis initiation site to the less substituted olefin (that appended to the aromatic portion of the molecule) and, thus, encourage macrocyclization to occur in preference to the alternative and undesired spirocycle formation. To begin testing this premise, monoprenylated **42c** was subjected to our standard olefin metathesis conditions (30 mol % catalyst **A**/refluxing dichloromethane) for 18 h (Scheme 8A). Remarkably, the desired macrocycle **43** was isolated from this reaction, albeit in a much reduced yield (30%), and, as a result, our knowledge of the scope of olefin metathesis, as a means to cyclize medium-sized rings, was now well and truly expanding. Indeed, few of those involved in its discovery and development could have predicted the true power of this synthetic tool[30] when it first emerged some decades ago.[31]

Despite being gratified by the successes we had achieved with these olefin metathesis reactions, we were becoming more and more perturbed by the problems arising from the presence of the tricarbonyl unit in our substrates. As mentioned earlier, this structural motif leaves a lot to be desired in terms of stability and ease of manipulation, and we felt that it might be a possible cause of the low yields we were obtaining for some of the metathesis reactions. We, therefore, opted to examine the protection of this fragile functionality as our next priority. To our surprise, this seemingly tangential move would pay considerable dividends in that it was set to reveal to us how we could control the access to both geometric isomers of the $\Delta^{16,17}$ macrocylic double bond.

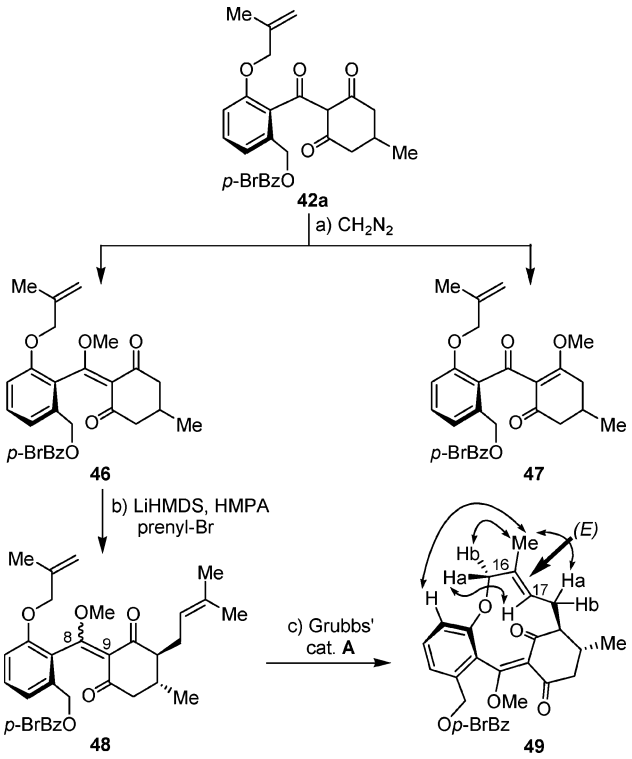
We chose to investigate protecting the tricarbonyl as its methyl vinylogous esters using diazomethane as we already had some experience in this approach, and, in addition, it was almost impossible to find other suitable protecting groups that would work in this very sterically encumbered environment. Thus, tricarbonyl compound **42a** (for the synthesis of **42a**, see Scheme 8A) was treated with diazomethane in diethyl ether at 0 °C, resulting in the formation of vinylogous ester **47**, which precipitated out of solution in 48% yield, and its sibling vinylogous ester **46** that was readily isolated from the residual solution in 48% yield (Scheme 9). The tricarbonyl unit in all of our previously synthesized substrates had always existed, for the most part, as the enol isomer(s) wherein the enol moiety was situated within the six-membered ring. This arrangement is most similar to the newly protected variant, methyl vinylogous ester **47**. We were curious to see if relocating this double bond to the exocyclic position, as in **46**, would have a bearing on the olefin metathesis reaction as it had changed the conformation of the molecule considerably, and so it was with vinylogous ester **46** that we decided to pursue our studies. Curiosity may have "killed the cat", but in our case it turned out to be the most valuable virtue which led to us solving the problem of how to efficiently synthesize both coleophomones B (**2**) and C (**3**). Alkylation of vinylogous ester **46** proceeded smoothly, using LiHMDS, HMPA, and prenyl bromide, to furnish the olefin metathesis precursor **48** (63%) as an inseparable mixture of $\Delta^{8,9}$ geometric isomers, each of which also existed as a 1:1 mixture of atropisomers (as revealed by ^{1}H NMR). Next, **48** was subjected to the action of Grubbs' catalyst **A** (20 mol %) in refluxing dichloromethane for a period of 20 h. Macrocyclization occurred (**48**→**49**, 30%), but this was not the main cause of our jubilation, for the newly formed macrocycle $\Delta^{16,17}$ double bond existed in the product **49** as a single isomer; however, this time it tantalizingly bore the *E*-configuration (see NOE relationships marked on structure **49**, Scheme 9). With this result in hand, we had now accessed both geometric isomers of the macrocycle $\Delta^{16,17}$ double bond and had thus gained significant insight into how we might specifically obtain both coleoph-

(29) For examples of olefins that are geminally disubstituted at the terminus participating in olefin metathesis reactions reported prior to our work,[6] see: (a) Nugent, W. A.; Feldman, J.; Calabrese, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 8992−8998. (b) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731−3734. (c) Braddock, D. C.; Wildsmith, A. J. *Tetrahedron Lett.* **2001**, *42*, 3239−3242. (d) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem.-Eur. J.* **2001**, *7*, 5286−5298. (e) Braddock, D. C.; Matsuno, A. *Tetrahedron Lett.* **2002**, *43*, 3305−3308. For examples of olefins that are geminally disubstituted at the terminus participating in olefin metathesis reactions reported after our work,[6] see: (f) Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem.* **2002**, *67*, 7946−7956. (g) Garcia-Fandiño, R.; Codesido, E. M.; Sobarzo-Sánchez, E.; Castedo, L.; Granja, J. R. *Org. Lett.* **2004**, *6*, 193−196.

(30) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.*, in press.

(31) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley−VCH: Weinheim, 2003; pp 161−206.

Scheme 9. Fourth Generation Approach: Stereospecific Formation of (*E*)-11-Membered Macrocycle **49** via Olefin Metathesis[a]



[a] Reagents and conditions: (a) excess CH_2N_2, Et_2O, 0 °C, 30 min, 48% of **46** plus 48% of **47**; (b) LiHMDS (1.05 equiv), THF/HMPA (10:1), −78 °C, 1 h; then prenyl-Br (2.0 equiv), −78 to 0 °C, 5 h, 63%; (c) cat. **A** (0.2 equiv), CH_2Cl_2, 40 °C, 20 h, 30% of **49** plus 35% recovered starting material **48**.

omones B (**2**) and C (**3**) using a route that diverged from a single precursor at a late stage. The transformation of **48** into **49** possessed one other beguiling feature related to the geometric isomers of the $\Delta^{8,9}$ double bond. The product **49** was the $\Delta^{8,9}$ *E*-isomer exclusively; in addition, a substantial amount of starting material was recovered (30%) that had been enriched in the $\Delta^{8,9}$ *Z*-isomer. We suspected that only the $\Delta^{8,9}$ *E*-isomer participated in the olefin metathesis macrocyclization reaction, although, at this stage, we had no definitive proof of this hypothesis because we could not separate the $\Delta^{8,9}$ geometric isomers of **48**. However, a subsequent investigation[32] looking at a series of similar compounds, where such a separation was possible, would prove that this assertion was indeed correct.

Olefin Metathesis and the Formation of the $\Delta^{16,17}$ *E*- and *Z*-Macrocycles of Coleophomones B and C

With so much new information, and the power of the olefin metathesis reaction, now revealed to us through our reconnaissance, we felt that we were in a particularly strong and exploitable position from which to tackle the synthesis of the macrocycle bearing coleophomones A−C (**1**−**3**). To this end, the fully substituted precursor **44b**, whose synthesis had only recently become feasible following the discovery of 4-DMAP's crucial role as an additive in the acyl cyanide coupling reaction with bisalkylated 1,3-cyclohexadiones (Scheme 8B), was protected using diazomethane under our previously established reaction conditions (Scheme 10). From this protection reaction, we were able to isolate and, significantly, separate each of the three possible regioisomers of the methyl vinylogous ester product (**50**, **51**, and **52**), in high overall yield (96%). Both of the vinylogous ester regioisomers situated within the six-membered ring, **50** and **52** (obtained with a yield of 32% and 16%, respectively), existed in a single form, whereas regioisomer **51** (obtained in 48% yield) proved to be an inseparable mixture of $\Delta^{8,9}$ geometric isomers (1.3:1) as expected, and each of these last two isomers also existed as a mixture of atropisomers (ca. 1:1 by ^{1}H NMR spectroscopy). Understandably, the endocyclic vinylogous ester **52** was the minor regioisomer isolated from this reaction due to its greater steric congestion around the quaternary center of the six-membered ring.

Upon exposure of all three regioisomers (**50**, **51**, and **52**), independently, to Grubbs' catalyst **A** (10 mol %), each one remarkably succumbed to a regio- and stereospecific ring-closing metathesis reaction, to furnish macrocycles **53**, **54**, and **55**, respectively, in high yields (**53**, 80%; **54**, 86%; **55**, 67%, Scheme 10). The products, **53** and **55**, arising from the metathesis of the endocyclic vinylogous ester regioisomers, **50** and **52**, both possessed exclusively the *Z*-configuration at the newly formed macrocyclic $\Delta^{16,17}$ double bond (see NOE interactions marked in Scheme 10). The product **55** of the more congested endocyclic vinylogous ester **52** existed as a single isomer with no spectroscopic evidence of atropisomerism. By contrast, macrocycle **53** existed as a 4:1 mixture of atropisomers in $CDCl_3$ (by ^{1}H NMR spectroscopy); however, it too collapsed to a single isomer when dissolved in CD_3CN (by ^{1}H NMR spectroscopy). The configurational details of macrocycle **53** were confirmed, and its precise solid-state structure was determined, by X-ray crystallographic analysis of a suitable crystal (see Figure 4).[33]

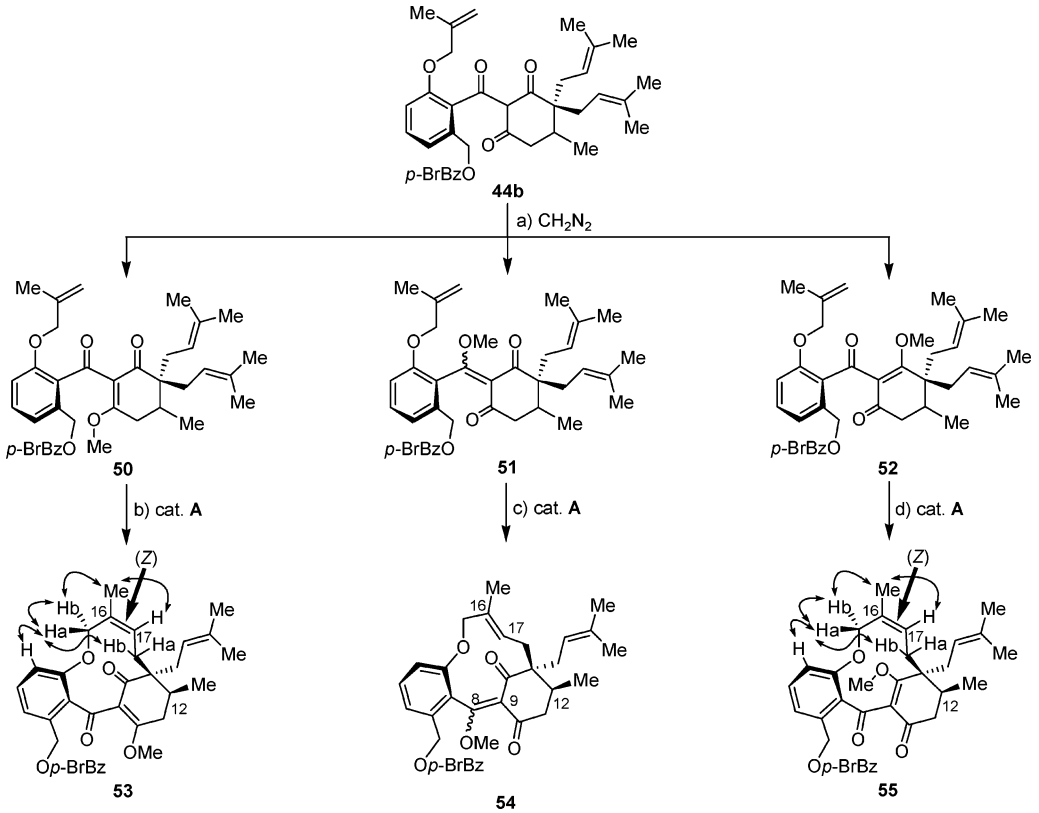
The NMR spectra obtained for olefin metathesis product **54** bore many more degrees of complexity in comparison to its siblings, **53** and **55**, and, as a result, some additional deduction was required to deconvolute many of its structural characteristics. The ^{1}H NMR spectrum clearly revealed that **54** existed as two inseparable isomers (1:1). Based on the two facts that, first, the starting material existed as a 1.3:1 mixture of $\Delta^{8,9}$ geometric isomers, and, second, the reaction yield was 86%, we surmised that the two isomers seen in the ^{1}H NMR spectrum were the $\Delta^{8,9}$ geometric isomers. This result was somewhat surprising in that, in contrast to the monoprenylated model system (**48**→**49**, Scheme 9), it indicated that in this case both the $\Delta^{8,9}$ *E*- and *Z*-isomers participated in the olefin metathesis reaction. Following on from this analysis, we deduced that the newly formed macrocyclic $\Delta^{16,17}$ double bond was present in just one isomeric form. Based on the result of our model study employing an exocyclic methyl vinylogous ester (**48**→**49**, Scheme 9), we hoped that this $\Delta^{16,17}$ double bond was the *E*-configured variant. At this stage, however, we had only a few scant, but tantalizing, clues garnered from ^{1}H NMR comparisons and inconclusive NOE studies that this might indeed be the case.

The olefin metathesis had been a resounding success, not only because of its exquisite specificity, which had seemingly

(32) Vassilikogiannakis, G.; Margaros, I.; Tofi, M. *Org. Lett.* **2004**, *6*, 205−208.

(33) CCDC-187043 contains the supplementary crystallographic data for compound **53**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB21 EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Scheme 10. Fourth Generation Approach toward the Coleophomones: Stereospecific Key Olefin Metathesis of Regioisomeric Vinylogous Esters **50**, **51**, and **52**[a]



[a] Reagents and conditions: (a) excess CH_2N_2, Et_2O, 0 °C, 1 h, 32% of **50**, 48% of **51** plus 16% of **52**; (b) cat. **A** (0.1 equiv), CH_2Cl_2, 40 °C, 3 h, 80%; (c) cat. **A** (0.1 equiv), CH_2Cl_2, 40 °C, 3 h, 86%; (d) cat. **A** (0.1 equiv), CH_2Cl_2, 40 °C, 4.5 h, 67%.

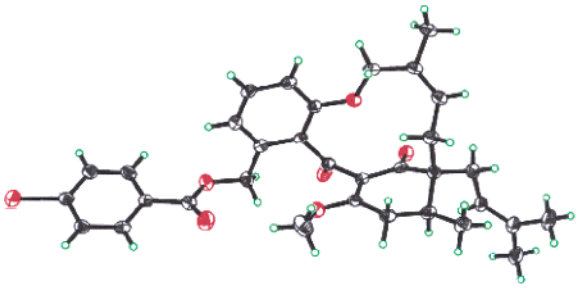


Figure 4. ORTEP representation of **53**.

delivered into our hands both of the requisite $\Delta^{16,17}$ macrocycle variants (corresponding to the two different coleophomone macrocycle skeletons), but also because the reaction yields were, without exception, much higher than we had obtained in the preceding model studies. Usually, one may expect reaction yields to decrease on going from a transformation involving simplified model compounds to one employing more complex real systems; however, in this case, the opposite appeared to be true. We rationalized that the presence of a second prenyl group forced an additional element of rigidity onto the metathesis precursors (**50**−**52**), making the loss in entropy upon macrocyclization less costly.[34] Furthermore, our modeling suggested that the most favorable molecular conformation adopted by the precursors bearing the second prenyl group (**50**−**52**) positioned the two reacting double bonds in close promixity to one another with less freedom to move and adopt new conformations where this proximity effect was not in play. We assumed that the metathesis reaction was irreversible due to the fact that we did not observe the formation of any spirocyclic products (analogous to compound **45**, Scheme 8).

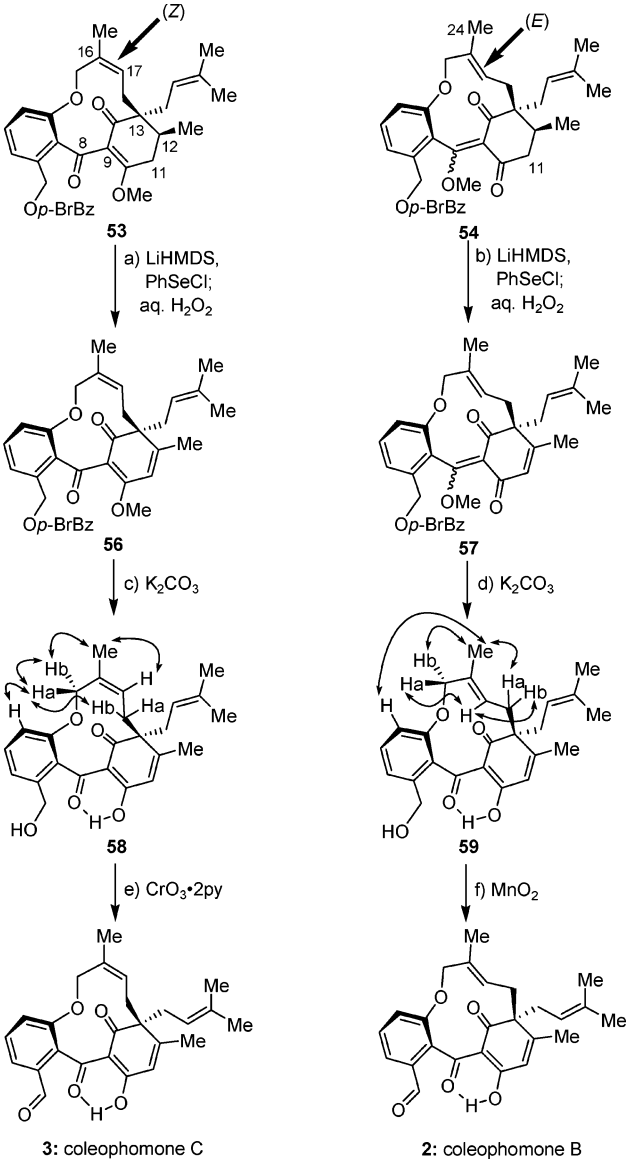
Our fascination with this puissant reaction did not end here, for it had yet another captivating feature; the reaction was completely diastereoselective, only the prenyl group occupying the position cis to the adjacent methyl (at C-12) participates in the olefin metathesis reaction. This preference presumably arises from the fact that the observed ring closure places the remaining prenyl group trans to the C-12 methyl substituent in the macrocyclic product, thus allowing both substituents to occupy the energetically more favorable equatorial positions of the cyclohexyl ring.

Finally, we were able to incontrovertibly prove our earlier hypothesis that the presence of an unprotected tricarbonyl motif was detrimental in the olefin metathesis reaction, by subjecting the unprotected precursor **44b** to Grubbs' catalyst **A**. The macrocyclization of this substrate (**44b**) occurred in only very modest yield (<20%), an exceedingly poor performance when compared to the momentous one of its protected derivatives (**50**−**52**) subjected to identical conditions.

The Final Lap − Completing the Synthesis of Coleophomones B (2) and C (3). In operatic terms, the drama had climaxed, and now it was time for the denouement; following just a few simple (at least on paper) synthetic operations, we

(34) For insightful discussion into the effects of entropy in the olefin metathesis reaction and examples, see: (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942−3943. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792−803. (c) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215−8230. (d) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117−3125.

Scheme 11. Fourth Generation Approach: Completion of the Total Synthesis of Coleophomones B (**2**) and C (**3**)[a]



[a] Reagents and conditions: (a) LiHMDS (1.3 equiv), THF, −78 to −10 °C, 1 h; then PhSeCl (1.4 equiv), −78 to 0 °C, 30 min; then sat. NH_4Cl (excess), 31% aqueous H_2O_2 (excess), 25 °C, 1 h, 61%; (b) LiHMDS (1.3 equiv), THF, −78 to 25 °C, 1 h; then PhSeCl (1.4 equiv), −60 to 25 °C, 30 min; then sat. NH_4Cl (excess), 31% aqueous H_2O_2 (excess), 25 °C, 1 h, 53%, plus 15% recovered **54**; (c) K_2CO_3 (3.0 equiv), MeOH, 25 °C, 11 h; then H_2O (excess), 3 h, 90%; (d) K_2CO_3 (3.0 equiv), MeOH, 25 °C, 40 min; then H_2O (excess), 30 min, 96%; (e) py (12 equiv), CrO_3 (6.0 equiv), CH_2Cl_2, 0 to 25 °C, 20 min; then **58**, 25 °C, 2 h, 81%; (f) MnO_2 (20 equiv), Et_2O, 36 °C, 8 h, 73%. py = pyridine.

hoped to have synthetically derived coleophomones B (**2**) and C (**3**) in our hands. From there, we anticipated no problems in delivering coleophomone A (**1**) shortly thereafter based on the literature precedent for the conversion of coleophomone B (**2**) into coleophomone A (**1**).[4] The first task of this home stretch was to install a double bond into the six-membered ring between carbons 11 and 12 (Scheme 11). This task was accomplished in both major series (i.e., starting from **53** and **54**) through a one-pot phenylselenide formation/oxidation/*syn*-elimination sequence, affording the α,β-unsaturated products **56** and **57**, in overall yields of 61% and 53%, respectively. The endocyclic vinylogous ester product **56** was, unsurprisingly, still a single compound, while the exocyclic vinylogous ester **57** remained as a mixture of $\Delta^{8,9}$ geometric isomers. However, the ratio of $\Delta^{8,9}$ geometric isomers in **57** had become enriched in favor of the *E*-variant, it now being 3:1 (*E*:*Z*) having started as a 1:1 mixture in **54**. Furthermore, the starting material **54** recovered from this reaction (15%) contained a higher proportion of the $\Delta^{8,9}$ *Z*-isomer. Molecular modeling combined with NOE studies led us to postulate that this result was due to the additional steric encumbrance experienced by the C-11 methylene group in the *Z*-isomer of **54**, caused by the direct positioning of the C-24 methyl group above it.

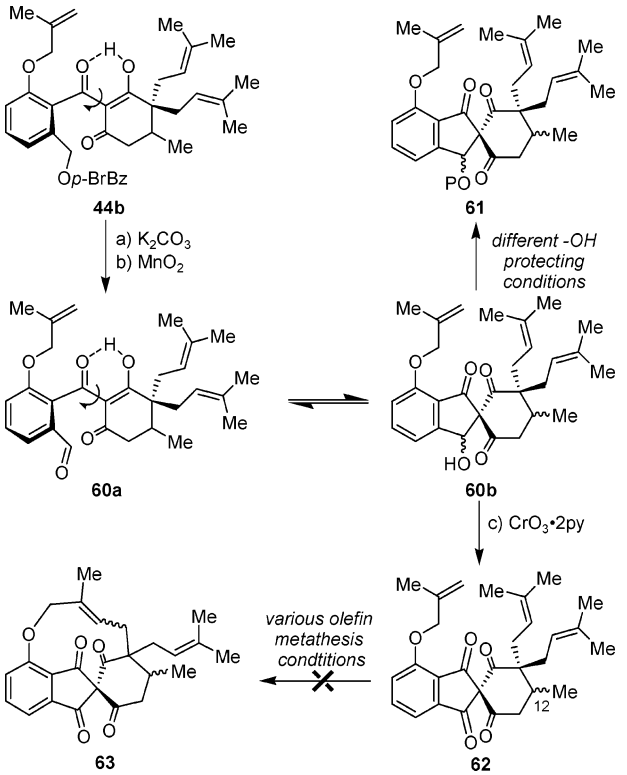
Brief exposure at ambient temperature of **56** and **57**, independently, to a methanolic potassium carbonate solution led to the global deprotection of these compounds. Vinylogous ester **56** took longer to complete the desired reaction set (3 h) and furnish **58** (90% yield) than did vinylogous ester **57**, which took just 30 min to afford **59** (96% yield). Conveniently, both products (**58** and **59**) had now coalesced into a single isomeric state, the structural intricacies of which yielded much more readily to thorough examination than those of some of the preceding isomeric mixtures. At this juncture we were, therefore, able to unequivocally confirm our earlier distinction between the $\Delta^{16,17}$ macrocyclic double bond *E*- and *Z*-geometric isomers, because **58** and **59** were not identical, and the only remaining possible difference between them was the $\Delta^{16,17}$ double bond geometry. As we had expected, the deprotected tricarbonyl compound **59** bore the *E*-configuration at the $\Delta^{16,17}$ macrocyclic double bond (for NOE interactions in **58** and **59**, see Scheme 11). For the final flourish, compound **59** was oxidized using MnO_2 in refluxing ether to afford coleophomone B (**2**) in good yield (73%). Compound **58**, however, reacted sluggishly with MnO_2 and was, therefore, oxidized to coleophomone C (**3**) using freshly prepared Collins reagent instead (the yield of this latter reaction being 81%). The icing on the cake for the last two steps of this conquest had been the spectroscopic purity of the products, **58**, **59**, **2**, and **3**, obtained from the specially devised acid−base workup, which rendered column chromatography superfluous and unnecessary. The full spectroscopic data of both synthetic coleophomone B (**2**) and C (**3**) were in every way identical to those reported for their naturally occurring counterparts.[1]

Attempted Synthesis of Coleophomone A

Attempts To Convert Coleophomone B (2) to Coleophomone A (1). With the synthesis of coleophomone B (**2**) now completed, we moved on to the new goal of converting it into coleophomone A (**1**), the third of our original four natural product targets.

The Merck discovery team had originally reported[4] that "coleophomones A and B exist in equilibrium with each other under physiological conditions," a statement possessing few details, which was, fortunately, qualified in a footnote wherein they added, "**1** and **2** [coleophomones A and B, respectively] exist in equilibrium in CH_3CN/water mixtures. The equilibrium strongly favors **2** at pH ≥ 7. The half-life of **1** at pH 7.5 is 5 min. Interconversion does not occur at pH < 3." We were unable to find a CD_3CN-D_2O ratio in which dissolved synthetic coleophomone B (**2**) showed even traces of conversion to coleophomone A (**1**) by ^1H NMR spectroscopy, despite the fact that we also examined a full range of pH values by making and then employing a series of buffered D_2O standards.

Scheme 12. Abortive Attempts To Synthesize Coleophomone A[a]



[a] Reagents and conditions: (a) K_2CO_3 (2.2 equiv), MeOH, 25 °C, 12 h; then H_2O (excess), 30 min, 64%; (b) MnO_2 (10 equiv), Et_2O, 36 °C, 15 h, 82%; (c) py (12 equiv), CrO_3 (6.0 equiv), CH_2Cl_2, 10 min; then **60**, 0 to 10 °C, 5 min, 39%.

Furthermore, we investigated these solutions over a broad time range (from 1 min to 24 h post preparation). Confused by our inability to find conditions under which coleophomone B (**2**) showed even the slightest propensity to undergo the requisite aldol reaction to form coleophomone A (**1**), we appealed to Shionogi and Merck for samples of the naturally obtained coleophomones. Both groups were forthcoming, and we were soon gratefully in possession of small quantities of coleophomones A (**1**) and B (**2**). Shionogi[1] and Merck[4] had both previously described the quantitative transformation of coleophomone A (**1**) into coleophomone B (**2**) upon treatment of the former with a base, a procedure we found eminently reproducible even under the mildest of conditions. However, the reverse reaction continued to elude us. At this point, we considered the conversion of coleophomone B (**2**) into coleophomone A (**1**) to be too shrouded in mystery to continue down this path, and hence we opted to pursue another proposal, the de-novo synthesis of coleophomone A (**1**).

Attempts To Synthesize Coleophomone A (1) Directly. The ease with which coleophomone A (**1**) could be converted to its open form congener, coleophomone B (**2**), through a retro-aldol reaction suggested to us that the spirocycle of **1** was highly strained and susceptible to opening. This deduction, combined with the reluctance of coleophomone B (**2**) to undergo the desired aldol reaction to form coleophomone A (**1**), led us to propose closing, and, then, protecting the spirocycle moiety of the molecule prior to macrocycle formation at a stage when the structure generally had fewer strains and congested sites.

To this end, we returned to the previously synthesized olefin metathesis precursor **44b** (Scheme 12). The *para*-bromobenzoate group of **44b** was hydrolytically removed (K_2CO_3, MeOH) in a somewhat problematic reaction (yield 64%), the difficulties arising from the insolubility of the tricarbonyl's potassium salt in a variety of solvent systems (K_2CO_3 deprotonates the tricarbonyl system forming the potassium salt). The primary benzylic alcohol, obtained from this basic hydrolysis of **44b**, was oxidized using manganese dioxide in refluxing ether to afford a complex mixture of isomeric products **60** (82%). The complexity of the mixture so-obtained (**60a**:**60b**, 1:1.6 in $CDCl_3$) was derived from the presence of at least two enol tautomers of the open isomer **60a**, existing alongside all possible stereoisomers in the closed isomer **60b** in a dynamic equilibrium. Not only was spectroscopic analysis difficult, but manipulation, reaction monitoring, and purification of this mixture (i.e., removal of byproducts, inability to separate components due to the aforementioned rapid equilibration) were all exceedingly troublesome. We decided to press ahead despite the problems, and we attempted to trap out the closed spirocyclic form **60b** by protection of its secondary benzylic alcohol to furnish spirocycle(s) **61**. We quickly found that no protection reaction using basic conditions could be employed, because under these conditions the open form of the starting material (**60a**) predominated and the reactions merely furnished products wherein the protecting group had been situated on one of the possible enol groups, or we recovered starting material and/or decomposed material. Under nonbasic conditions, modified versions of standard procedures, a range of protecting groups were tested: triethylsilyl (TES−OTf:Et_3N, 1.2:1.1 equiv), methoxymethyl (MOM-Cl:Hünig's base, 2:1.8 equiv), *para*-bromobenzoate (*p*-BrBz:Et_3N, 1.5:1.4 equiv), acetate (AcCl:Et_3N, 1.2:1.1), and methyl (Meerwein's salt BF_4OMe_3:proton sponge, 1.5:1.3, or excess diazomethane). Degradation and/or preferential protection of the tricarbonyl unit were seen under most of these reaction conditions. The triethylsilyl-protection did succeed, albeit in poor yield, only to furnish an unstable product where migration of the silyl group led to rapid decomposition of the material. This migration-degradation sequence occurred even on TLC (thin-layer chromatography) plates and, therefore, rendered this protecting group unusable. Methyl protection, using Meerwein's salt and proton sponge, furnished **61** (P = Me) in 13% yield alongside the products of the regioisomeric protection of **60** as its vinylogous esters and the recovery of starting material. However, when this scant material (**61**, P = Me) was subjected to our standard olefin metathesis conditions, no traces of successful macrocyclization could be detected whatsoever.

At this point, we wondered whether the spirocycle's inherent strains would preclude the desired olefin metathesis reaction altogether, so we decided to investigate this reaction as a priority. The obvious substrate for such an examination was compound **62**, wherein the spirocycle had been locked shut by an oxidation reaction. Spirocycle **62** was, therefore, synthesized by oxidation of **60** using Collins reagent (CrO_3•2py). As we had come to expect for the reactions of **60**, the oxidation proceeded in poor yield (39%). Furthermore and unfortunately, despite the testing of a broad range of olefin metathesis conditions (including testing several different catalyst systems, varying solvents, and using microwave or thermal assistance), no macrocylization was ever observed. Bearing in mind the speed with which coleophomone A (**1**) unravels to give coleophomone B (**2**), we felt the

inherent strain of the former compound was just too great a hurdle for the desired olefin metathesis reaction, and we regretfully concluded that the limits of this approach had been reached. In addition, the difficulty we had encountered in securing the closed spirocyclic forms of these compounds (possessing no macrocycle to add to the strain) in reasonable yields added to the mystique surrounding the Merck team's reported[4] conversion of coleophomone B (**2**) to coleophomone A (**1**). What seemed to be beyond doubt, however, was that the synthesis of coleophomone A (**1**) would require a completely redesigned strategy and, therefore, constituted another separate project for consideration sometime in the future.

Unveiling Some of the Intricacies of the Coleophomone Olefin Metathesis Macrocycle Formation Reaction. The more we examined the results from our investigations described thus far, the more the olefin metathesis reaction stood out as a remarkable chemical achievement. It was a reaction with so many intriguing subtleties that we wanted to understand in greater detail. For example, we were curious about the origin of the extraordinary selectivity that was observed wherein only one geometric isomer of the macrocycle's new olefin ($\Delta^{16,17}$) was formed in each reaction; in addition, what were the factors that precipitated the clean and complete switch in this selectivity from *E*- to *Z*- on going from one substrate to the next? Furthermore, central to our strategy had been the use of a bisprenylated 1,3-cyclohexadione, introduced based on our hypothesis that this choice of substitution pattern would induce initiation of the metathesis to occur solely at the 2-methylallyl olefin attached to the aromatic domain of the molecule and, thus, lead to preferential macrocyclization over the possible alternative, spirocyclization. The veracity of this postulate needed investigation. As a result, we decided to undertake some further studies aimed at deciphering certain secrets of the olefin metathesis reaction, within this context, including its key features, and its scope.

An eye for detail will have led the reader to appreciate that the coleophomone synthesis was complicated at many stages by a proliferation of isomers (regio-, atrop-, and stereo-). To circumvent problems arising from the latter in our ensuing studies, we opted to exorcise the C-12 methyl group from our model substrates. Thus, six model substrates, **67a**−**69a** and **67b**−**69b**, were synthesized, starting from 1,3-cyclohexadione (**64**) and using our established reaction set, to allow us to investigate the outcome of different olefin combinations in the metathesis reaction (Scheme 13). On subjecting these substrates to the action of Grubbs' catalyst **A** in refluxing CH_2Cl_2, and following isolation of the products of the ensuing reaction, we were to learn a great deal about olefin metathesis in general.

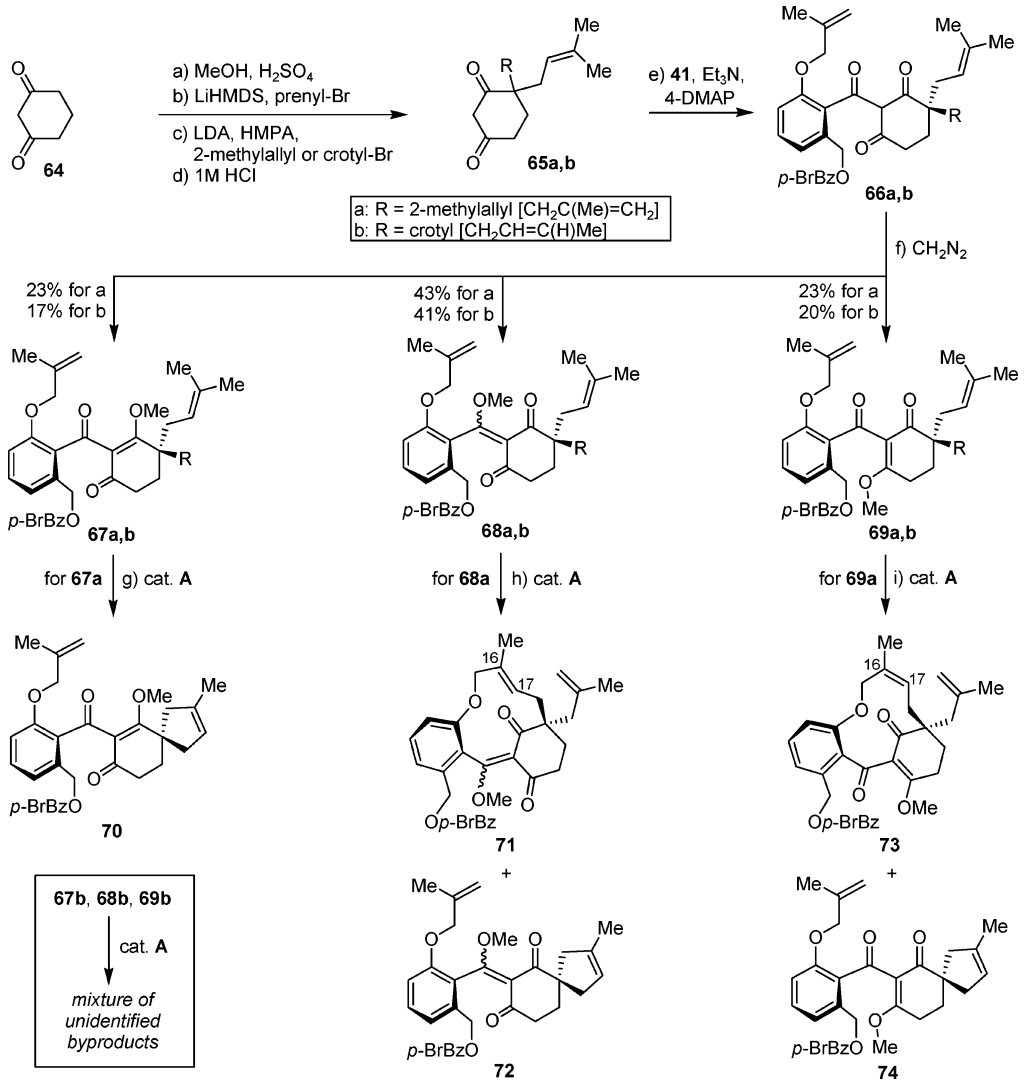
Beginning with the results for the series of compounds where one prenyl group had been replaced with a 2-methylallyl substituent (substrates **67a**−**69a**), when the vinylogous ester **67a** was subjected to the standard olefin metathesis conditions for 4 h, a single spirocyclic product, **70**, was isolated in 67% yield. None of the macrocyclic alternative was isolated from this particular reaction. Based on the later results that we will discuss below, we felt that the macrocycle may have formed only to succumb to rapid conversion into the spirocycle **70** via a second metathesis reaction; however, this explanation remains conjecture. If this metathesis precursor, **67a**, is compared to the corresponding coleophomone substrates (**50**−**52**), it can be seen that there are now two potential initiation sites (both of the two 2-methylallyl functionalities) as opposed to just one (under our reaction conditions, we never observed any indication, such as spirocycle formation in the bisprenylated olefin metathesis substrates, that initiation could occur at a prenyl group). Our rationale would have it that it is initiation taking place at the 2-methallyl group on the 1,3-cyclohexadione of **67a** that affords the spirocyclic product **70** directly; however, initiation at the other 2-methallyl group may also give **70** after a second metathesis reaction and via the macrocyclic intermediate. The results obtained from the metathesis of **68a** upheld and extended the inferences we had made up to this point. Vinylogous ester **68a** yielded two products, the macrocycle **71**[35] and the spirocycle **72** (10% and 65%, respectively), from its metathesis reaction. Like **67a**, **68a** has two possible sites for initiation, and, once again, we propose that the macrocycle **71** forms preferentially when initiation occurs at the 2-methylallyl group attached to the aromatic portion of the molecule, while the spirocycle **72** forms when initiation occurs at the other 2-methylallyl group (or when the macrocycle **71** is opened by a second metathesis reaction, vide supra). The macrocycle **71** contains the new trisubstituted olefin ($\Delta^{16,17}$), as opposed to the possible alternative of a tetrasubstituted double bond ($\Delta^{16,17}$). This result is not at all surprising given the difficulty olefin metathesis appears to have in forming such tetrasubtituted double bonds, as evidenced by scant representation in the literature;[36] however, it does open the molecule up to an interesting new reaction path. If this olefin metathesis reaction was permitted to run for 48 h, rather than just until the disappearance of the starting material by TLC (as in the previous cases), none of the macrocycle **71** was isolated; instead spirocycle **72** was the sole product, obtained with only a marginal reduction in the yield (50%).

Recalling that in the case of the real coleophomone systems (**53**−**55**, Scheme 10) we had concluded that the macrocyclization was irreversible because no spirocycle formation was ever seen even after long periods of exposure to catalyst **A**, we sought an explanation for our current observation. Our rationale was as follows: the trisubstituted olefins formed in these reactions are, essentially, stable to the reaction conditions; they only show slight degradation as a consequence of very prolonged exposure to the catalyst. This assertion breaks down, however, when the product still retains a possible metathesis initiation site. For example, macrocycle **71** (Scheme 13) has a pendant 2-methylallyl group, and we suggest it is this group that makes the macrocycle **71** less stable in comparison to macrocycles **53**−**55**, for the olefin metathesis catalyst (now bearing a $=C(CH_3)_2$ carbene group rather than the original =CHPh group, because it has already participated in the metathesis catalytic cycle) can insert into this 2-methylallyl olefin and from here intramolecularly cleave the macrocycle, and, in so doing, form the

(35) The $\Delta^{16,17}$ double bond geometry was assigned for compounds **71** and **73** on the basis of the direct comparison of ^1H and ^{13}C NMR spectral data obtained for these compounds with that obtained for the corresponding coleophomone metathesis products.

(36) For selected examples of olefin metathesis being used to form tetrasubstituted double bonds, see: (a) Hoye, T. R.; Jeffrey, C. S.; Tennakon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210−10211. (b) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74−75. (c) Anastasia, L.; Dumond, Y. R.; Negishi, E. *Eur. J. Org. Chem.* **2001**, 3039−3043. (d) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (e) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787−4790.

Scheme 13. Olefin Methathesis of Model Compounds **67a**,**b**, **68a**,**b**, and **69a**,**b**: Formation of Spirocycles **70**, **72**, and **74**[a]



[a] Reagents and conditions: (a) concentrated H_2SO_4 (cat.), MeOH, 65 °C, 12 h, 88%; (b) LiHMDS (1.05 equiv), THF, −78 °C, 1 h; then prenyl-Br (1.1 equiv), −78 to 0 °C, 3 h, 85%; (c) LDA (1.1 equiv), THF, slow addition of a solution of starting material in THF:HMPA (7:1), −78 °C, 1 h; then 2-methylallyl or crotyl-Br (2.0 equiv), −78 to 20 °C, 12 h, 78%; (d) 1 M HCl:THF (1:10), 25 °C, 14 h, 92−95%; (e) **41** (1.1 equiv), Et_3N (2.0 equiv), 4-DMAP (1.0 equiv), THF, 25 °C, 96 h, 81% of **66a** and 83% of **66b**; (f) excess CH_2N_2, Et_2O, 0 °C, 1 h, 23% of **67a** plus 43% of **68a** plus 23% of **69a** while 17% of **67b** plus 41% of **68b** plus 20% of **69b**; (g) cat. **A** (0.2 equiv), CH_2Cl_2, 40 °C, 4 h, 67%; (h) cat. **A** (0.2 equiv), CH_2Cl_2, 40 °C, 8 h, 65% of **72** plus 10% of **71** while only 50% of spirocycle **72** after 48 h at 40 °C; (i) cat. **A** (0.2 equiv), CH_2Cl_2, 40 °C, 3 h, 50% of **74** plus 21% of **73** while only 41% of spirocycle **74** after 48 h at 40 °C.

thermodynamically more stable spirocycle **72**. This hypothesis provides a feasible explanation for the product distribution obtained from the metathesis of all of the substrates **67a**−**69a** (and **67b**−**69b**, see below) and explains why no spirocycle was ever observed in the metathesis reactions of the coleophomone substrates **50**−**52** (Scheme 10). The results obtained for the metathesis of vinylogous ester **69a** mirror those obtained and, as already discussed, for **68a**, with the exception that the other geometric isomer of the new $\Delta^{16,17}$ double bond (this time the *Z*-isomer) is formed in its macrocyclic product **73**, in accord with our coleophomone precedent. The precise reasons why changing the position of the vinylogous ester from endocyclic to exocyclic caused a complete switch in selectivity were not found in these studies, or from the molecular modeling of the coleophomone systems that we undertook at this time. A later investigation,[32] however, revealed that the use of the *para*-bromobenzoate as a protection for the benzylic alcohol lay at the heart of this issue.

Moving on to the substrates **67b**−**69b** (Scheme 13) where a prenyl group had been replaced with a crotyl group (predominantly in the trans form), all of these substrates, when subjected to our standard metathesis conditions, decomposed producing a mixture of unidentifiable products. We suggest that this complete degradation occurs because the crotyl olefin is now favored over the 2-methylallyl olefin alternative as the site for initiation. With initiation occurring on a substituent of the six-membered ring, rather than the aromatic portion of the molecule, no macrocyclization occurs; instead the spirocycle forms rapidly. We are confident that we have identified correctly this pathway as being dominant because the macrocycles formed from these substrates (**67b**−**69b**) would be the coleophomone type macrocycles **53**−**55**, (i.e. Scheme 10), which had previously been shown to be stable to the reaction conditions. The spirocycles proposed as initial products for these reactions contain disubstituted double bonds within the newly formed five-membered rings; these bonds are rapidly cleaved by the olefin metathesis

catalyst, and, from there onward, polymeric products begin to appear as degradation continues apace.

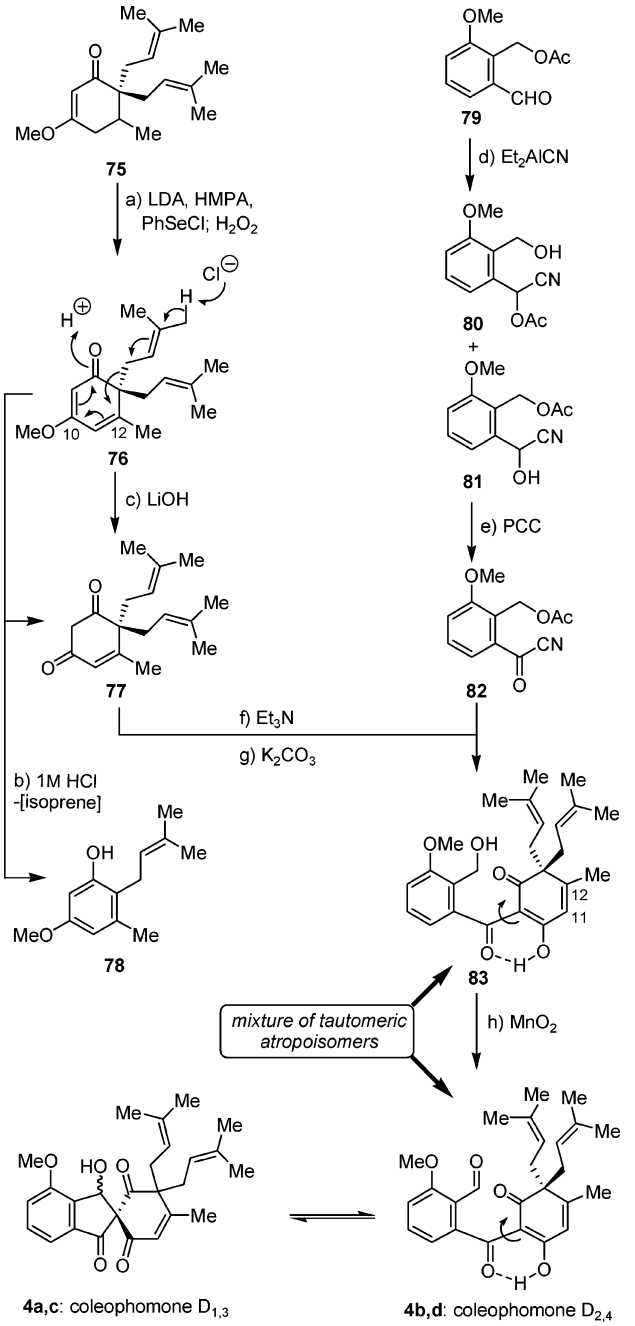
The above work very clearly suggests that the initiation of olefin metathesis reactions does not occur at prenyl groups (under the range of conditions we investigated), but a prenyl group may react in a metathesis reaction if prior initiation has occurred elsewhere in the molecule. Likewise, endocyclic trisubstituted double bonds are stable to the reaction conditions unless the same molecule bears a second appropriate initiation site. Furthermore, crotyl-type olefins become the initiation site of preference when the choice is between a 2-methylallyl group and a crotyl group. These results have, therefore, uncovered a clear order of preference for the initiation step of an olefin metathesis reaction using Grubbs' catalyst **A** and demonstrate how this information can be used to orchestrate a metathesis reaction such that one alternative mode of reaction is favored over another (e.g., macrocyclization over spirocyclization).[36a] In some cases, this option provides us the opportunity to design substrates that can override the natural bias for producing a lower energy product via a lower energy transition state (for example, one can construct strained macrocycles in preference to simple five-membered spirocycles).

Total Synthesis of Coleophomone D (4)

We hoped we had now accumulated all of the information necessary to smoothly synthesize the last remaining coleophomone family member, coleophomone D (**4**), thus bringing our coleophomone adventure to an auspicious conclusion. In the end, this confidence proved, at least for the substantial part, to be well placed as a successful synthesis was forthcoming. However, even the seemingly simple coleophomone D (**4**) molecule held several thorny traps into which the unwary could step and be caught. The proposed structure for coleophomone D (**4**), of course, bore the unique and opposite pattern of substitution about the aromatic ring from its sibling coleophomones A−C (**1**−**3**), and we were prepared, therefore, to find its structure had been wrongly assigned at the outset due to its unusual dynamic isomerism.

Because coleophomone D (**4**) does not contain a macrocycle, and, therefore, does not require an olefin metathesis reaction to complete its synthesis, we wanted to avoid the clumsy sequence of having to protect the tricarbonyl unit, at a late stage of the sequence, solely to introduce the $\Delta^{11,12}$ double bond, steps that would have to be followed by immediate deprotection. It seemed highly desirable, therefore, to introduce the $\Delta^{11,12}$ double bond into the six-membered ring while it was protected as the vinylogous ester for the purpose of the two C-13 alkylation reactions. To this end, the previously obtained vinylogous ester **75** was treated with LDA in the presence of HMPA as a key additive to form the γ-enolate, which was, in turn, quenched with PhSeCl (Scheme 14). Without isolation, the resulting crude selenides (diastereoisomers) were oxidized in situ by treatment with aqueous H_2O_2 at 45 °C for 1 h. This efficient one-pot reaction sequence afforded the rather labile vinylogous ester **76** in high overall yield (78%). Acidic hydrolysis of the vinylogous ester **76**, employing various conditions, always led to the predominant formation of the aromatic product **78**, accompanied by only meager amounts of the desired 1,3-cyclohexadione **77**. This unanticipated aromatization (**76**→**78**) must proceed via the initial protonation of **76** to afford a highly

Scheme 14. Total Synthesis of Coleophomone D[a]



[a] Reagents and conditions: (a) LDA (2.0 equiv), addition of a solution of **75** (1.0 equiv) in THF:HMPA (25:1), −78 to 0 °C, 2 h; then PhSeCl (1.5 equiv), −78 to 20 °C, 0.5 h; then 30% aqueous H_2O_2 (excess), 45 °C, 1 h, 78%; (b) 1 M HCl:THF (1:5), 25 °C, 48 h, 50% of **78** plus 30% of **77**; (c) LiOH·H_2O (5.0 equiv), MeOH:H_2O (2:1), 80 °C, 12 h, 91%; (d) Et_2AlCN (1.0 equiv), toluene, 0 °C, 2 h, 59% of **81** plus 15% of **80**; (e) PCC (4.0 equiv), CH_2Cl_2, 40 °C, 4 h, 51%; (f) **77** (1.0 equiv), **82** (1.0 equiv), Et_3N (1.0 equiv), THF, 25 °C, 72 h, 80%; (g) K_2CO_3 (3.0 equiv), MeOH, 25 °C, 24 h, 94%; (h) MnO_2 (10 equiv), Et_2O, 36 °C, 4 h, 83%.

stabilized allylic tertiary cation (at C-10 ↔ C-12), which is then subject to the loss of a proton and a molecule of isoprene to give the phenol **78**, as indicated in Scheme 14. We avoided this first ambush by developing a protocol for an alkaline hydrolysis of **76**, using LiOH in a methanol−water mix at 80 °C, which afforded **77** in high yield (91%).

To synthesize the acyl cyanide coupling partner **82**, we modified our existing set of reactions as is summarized below

and in Scheme 14. Aldehyde **79** was rapidly accessed starting from 1,2-dimethyl anisole using a known, two-step literature procedure.[37] Treatment of **79** with Nagata's reagent afforded the desired cyanohydrin **81** (59% yield) as the major product, accompanied by some of its regioisomer **80** (15%) wherein the acetate group had migrated. The mixture (**80** and **81**) was oxidized with PCC, and, following chromatographic separation, the relatively fragile acyl cyanide **82** was isolated in 51% yield. Acyl cyanide **82** was much more prone to decomposition via hydrolysis than the corresponding acyl cyanide **41** (Scheme 8), presumably due to its significantly reduced steric encumbrance. The fragility of **82** was set to cause some problems in the next step, the coupling of **82** and **77**. When we employed the conditions in this reaction that we had optimized for our previous substrates, **8b** and **41** (see Scheme 8b), hydrolysis competed with coupling, such that the yields of the desired tricarbonyl product were disappointingly poor. In a strange twist of chemical fate, the answer to this conundrum lay with the additive 4-DMAP. Just as the addition of 4-DMAP had made the coupling of **8b** and **41** possible, so its removal from the protocol held the key to making the coupling of **77** and **82** viable. Thus, **77** and **82** could be coupled successfully in the presence of one equivalent of Et_3N only, at ambient temperature, in a yield of 80%.

We were now only two steps away from coleophomone D (**4**). First, removal of the acetate protecting group was successfully achieved using methanolic K_2CO_3, to furnish **83** as a mixture of atropisomers in high yield (94%), and, second, oxidation of **83** with MnO_2 gave coleophomone D (**4**) in 83%. The ^1H and ^{13}C NMR spectra of synthetic coleophomone D (**4**) revealed the presence of all of the postulated isomers (D_1-D_4, **4a**−**4d**, Scheme 1) whose signals were in accord exactly with those reported by the Shionogi group,[3] thus demolishing the idea that the structure of coleophomone D (**4**) had been assigned wrongly and replacing it with the intriguing question of how nature synthesizes the coleophomones with their regioisomeric variation (vide supra). Until further studies are instigated, our current knowledge allows us only to imagine what the answer to this last question might be, speculation that we would rather avoid delineating prematurely at this juncture.

(37) Box, V. G. S.; Yiannikouros, G. P. *Heterocycles* **1990**, *31*, 1261−1270.

Conclusion

With the notable exception of coleophomone A (**1**) whose relationship to coleophomone B (**2**) and, as a direct result, whose synthesis had eluded us throughout this investigation, this concise total synthesis of coleophomone D (**4**) marked the completion of our originally defined task, that of completing total syntheses for the entire coleophomone family. The total syntheses of coleophomones B (**2**) and C (**3**) using a remarkable olefin metathesis reaction to form their highly strained and congested macrocycle had pushed the frontiers of this venerable reaction forward into a new domain. The successful coleophomone macrocycle synthesis reported herein illustrates just how powerful an ally the olefin metathesis reaction can be in forming constrained medium-sized (10−12 membered) rings. Furthermore, our ensuing studies had unveiled a number of the reaction's intricacies that may be gainfully employed in the future to design synthetic blueprints toward even more demanding synthetic targets.

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

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