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- [14] See Supporting Information for experimental details.
- [15] Preliminary results indicate that the allenylation reaction is also effective with aldehydes, as heating a solution of the cyclic vinylboronic acid **14** and α -triisopropylsilyloxy acetaldehyde in toluene at 60°C provides the homologated trisubstituted allene (ca. 50% yield, d.r. ca. 5:1:0:0).
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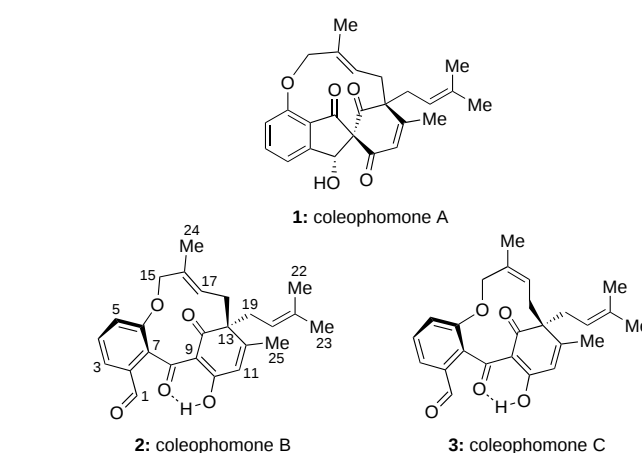


The Total Synthesis of Coleophomones B and C**

K. C. Nicolaou,* Georgios Vassilikogiannakis, and Tamsyn Montagnon

*Dedicated to Professor Thomas J. Katz
on the occasion of his 65th birthday*

In 1998, a patent^[1] from a group at Shionogi disclosed the structures and biological activity of three novel natural products, designated I-1 (**1**), I-2 (**2**), and I-3 (**3**), which had been isolated from a broth produced by the fungus *Stachybothys cylindrospora* RF-5900. Two of these compounds later re-emerged in the literature when a group at Merck discovered them in extracts from the fermentation of *Coleophoma* sp. fungi and named them coleophomones A (**1**) and B (**2**).^[2] The biological profile of the coleophomone family includes



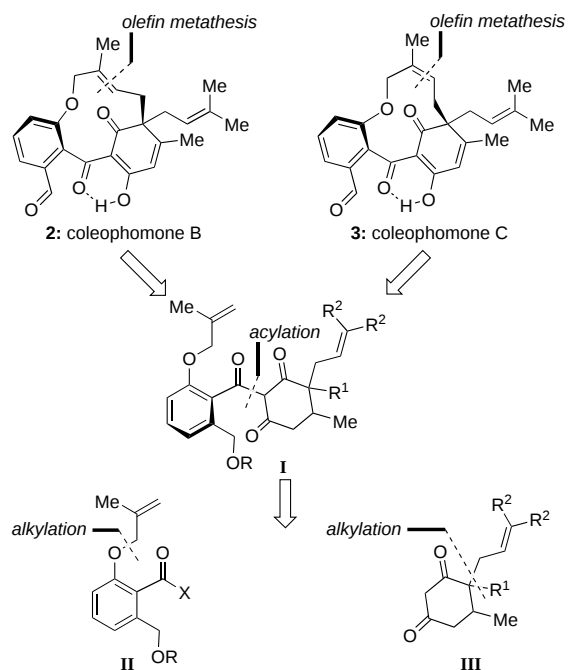
antifungal activity,^[1] inhibition of human heart chymase,^[1,3] and antibiotic properties.^[2] In addition, their unique molecular architectures are laden with unusual and challenging features: The strained and rigid framework of the coleophomones possesses a sensitive tricarboxyl moiety tethered into an 11-membered macrocycle whose strain is derived from the incorporation of a fused aryl ring and a highly unsaturated bridging six-membered carbocycle with the point of attachment being a quarternary carbon atom. Herein we report the total synthesis of coleophomones B (**2**) and C (**3**)^[4] by a route that pushes the frontiers of the olefin metathesis reaction as a means to construct challenging molecular complexity.

Coleophomone A (**1**) is related to coleophomone B (**2**) by an aldol reaction that affords, from the latter, the unique spirocycle seen in the former. In view of the reported^[2] interconversion of **1** and **2**, our approach to the coleophomone family initially focused on the total synthesis of **2** and **3**. These differ only in the configuration of the double bond ($\Delta^{16,17}$) that is *E* in **2** and *Z* in **3**. From all the possible retrosynthetic disconnections we therefore chose the one dissecting this double bond by the olefin metathesis reaction (Scheme 1). This disconnection, which led to the general precursor **I**, promised an exciting synthetic adventure because of the unprecedented nature of the challenge, made even more acute by the requirement to control the geometrical outcome of the projected ring-closing metathesis to deliver either isomer at will and the possible occurrence of atropisomers within the targeted frameworks. Our second major retrosynthetic disconnection operated on precursor **I** at the C8–C9 bond to generate the key building blocks **II** and **III**. This left the considerable hurdle of their union to be negotiated in the synthetic direction.

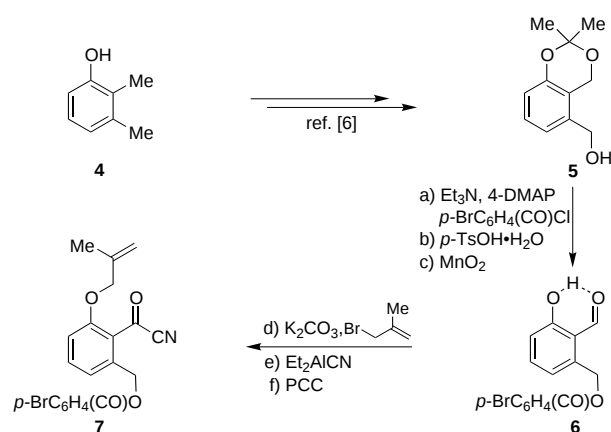
Scheme 2 summarizes the construction of the requisite aromatic building block **7**. The preference for the cyano group in **7** was based upon literature precedent regarding our subsequent intentions to effect preferential C-acylation over the usually more facile O-acylation in the coupling step,^[5] while the *p*-bromobenzoate group was chosen as a protecting group to enhance the chances for crystalline derivatives to be obtained for X-ray crystallographic analysis purposes. Thus, beginning with commercially available 2,3-dimethyl phenol (**4**) and following a five-step literature procedure,^[6] we arrived at hydroxy acetone **5**, whose conversion to benzaldehyde

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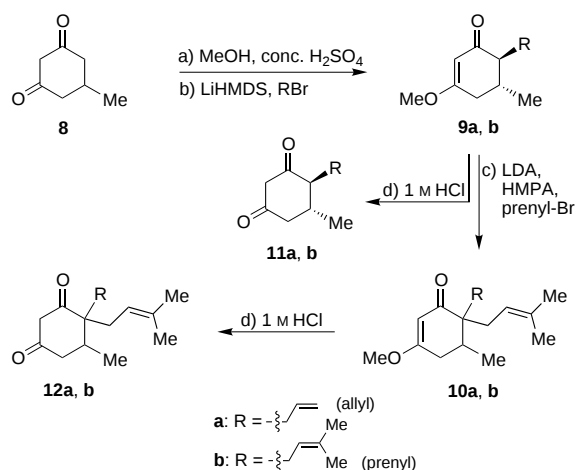
Scheme 1. Retrosynthesis of coleophomones B (2) and C (3).



Scheme 2. Construction of acyl cyanide 7. a) Et₃N (1.5 equiv), *p*-BrC₆H₄(CO)Cl (1.05 equiv), 4-DMAP (0.05 equiv), CH₂Cl₂, 25 °C, 20 min, 97%; b) *p*-TsOH·H₂O (0.3 equiv), THF/H₂O (3/2), 75 °C, 10 h, 85%; c) MnO₂ (10 equiv), EtOAc, 25 °C, 1.5 h, 87%; d) K₂CO₃ (2.0 equiv), 3-bromo-2-methylpropene (1.5 equiv), acetone, 56 °C, 2 h, 91%; e) Et₂AlCN (1.1 equiv), toluene, 0–25 °C, 1 h, 82%; f) PCC (4.0 equiv), CH₂Cl₂, 40 °C, 12 h, 73%. 4-DMAP = 4-dimethylaminopyridine; *p*-TsOH = *p*-toluenesulfonic acid; PCC = pyridinium chlorochromate.

derivative 6 entailed sequential *p*-bromobenzoylation, acetonide removal, and MnO₂ oxidation (72% yield over the three steps). Aldehyde 6 was then smoothly alkylated with 3-bromo-2-methylpropene in the presence of K₂CO₃ (91% yield) and subsequently converted to the desired acyl cyanide 7 by a two-step sequence involving initial addition of Nagata's reagent followed by PCC oxidation of the resulting cyanohydrin, events which proceeded in 60% overall yield.

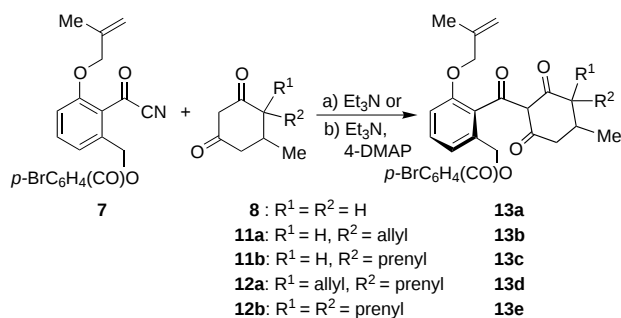
The desired 1,3-cyclohexadiones (**11a**, **11b**, **12a**, and **12b**) were synthesized starting with C₃-symmetrical 5-methyl-1,3-cyclohexadione (**8**) and following the divergent pathway shown in Scheme 3. Thus, methylation of **8** followed by



Scheme 3. Synthesis of substituted 1,3-cyclohexadiones **11a**, **11b**, **12a**, and **12b**. a) conc. H₂SO₄ (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), –78–0 °C, 3 h, 80–85%; c) LDA (1.1 equiv), THF, slow addition of a solution of **11a** or **11b** in THF/HMPA (7/1), –78 °C, 1 h; then prenyl-Br (2.0 equiv), –78–20 °C, 12 h, 89%; d) 1 M HCl/THF (10/1), 25 °C, 14 h, 95–98%. LiHMDS = lithium bis(trimethylsilyl)amide; LDA = lithium diisopropylamide.

alkylation of the LiHMDS-derived enolate with either allyl or prenyl bromide afforded the *anti* alkylated products **9a** and **9b**, respectively (80–85% yield). The bisalkylated congeners (**10a** and **10b**) were prepared by a second alkylation that proved more demanding than the first. These compounds were obtained in good yield (89%) by using HMPA as an additive and LDA as the base to generate the corresponding enolate (–78 °C) followed by addition of the allylic bromide (–78 °C) and slow warming of the reaction mixture to ambient temperature. Finally, deprotection of the resulting vinylogous methyl esters (**9a**, **9b**, **10a**, and **10b**) by aqueous acid hydrolysis furnished the coveted 1,3-cyclohexadiones (**11a**, **11b**, **12a**, and **12b**) in 95–98% yield.

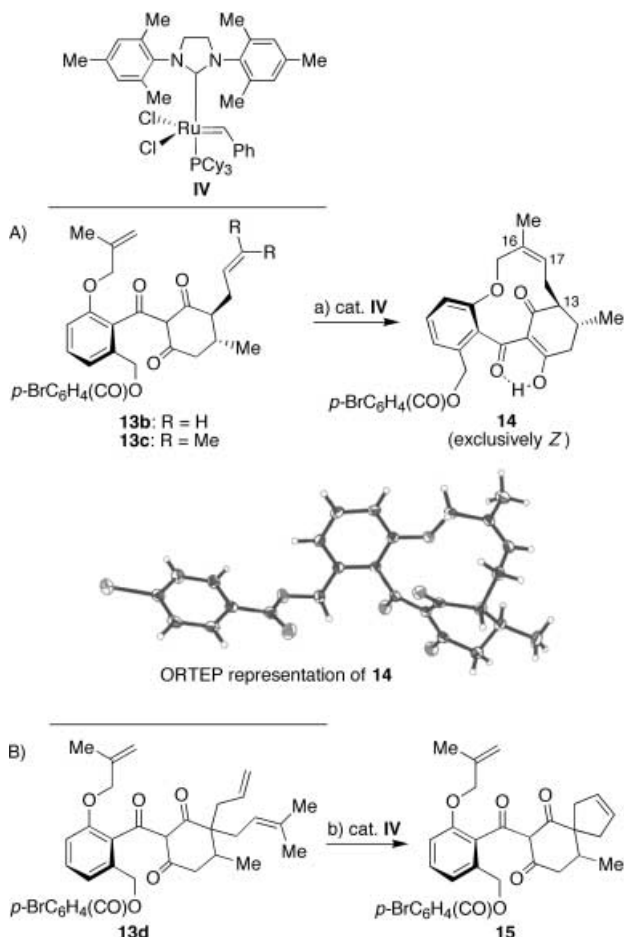
With all of the requisite building blocks in hand, the task now confronting us was the development of appropriate conditions to achieve the desired C-acylation reaction. Whilst smooth coupling took place (see Scheme 4) when the unsubstituted and monosubstituted 1,3-cyclohexadiones **8**, **11a**, and **11b** were combined with acyl cyanide **7** in the presence of Et₃N at ambient temperature to furnish **13a**



Scheme 4. Coupling of acyl cyanide 7 with various 1,3-cyclohexadiones. a) **8**, **11a**, or **11b** (1.2 equiv), Et₃N (2.0 equiv), THF, 25 °C, 6–12 h, 91–98%; b) **12a**, **12b** (1.2 equiv), Et₃N (2.0 equiv), 4-DMAP (1.0 equiv), THF, 25 °C, 72–96 h, 83–86%.

(98%), **13b** (94%), and **13c** (91%), respectively,^[7] the disubstituted substrates **12a** and **12b** proved recalcitrant, refusing to react even after prolonged reaction times under similar conditions. However, upon modification of the above protocol to include 4-DMAP, the coupled products **13d** and **13e** could be isolated after 72–96 h, in 83–86% yield (Scheme 4).

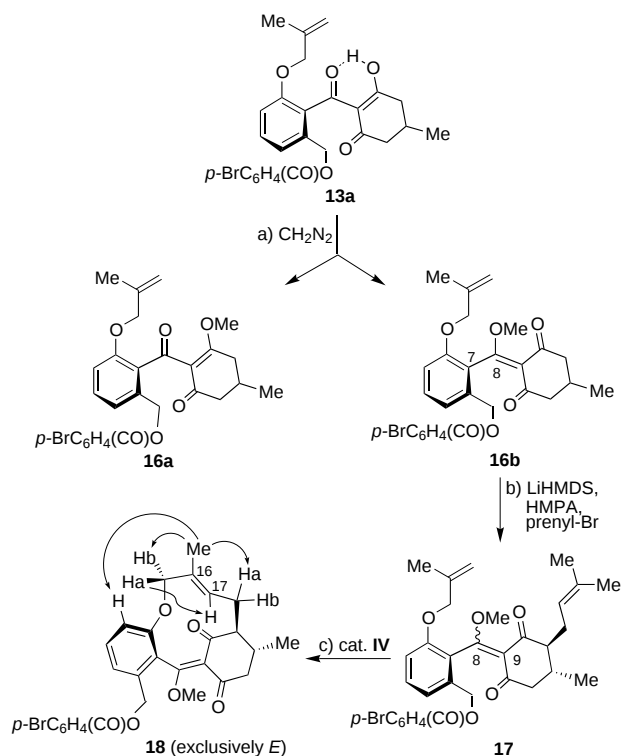
The scene was now set for the exploration to begin into the feasibility of the crucial olefin-metathesis-based step to forge the challenging 11-membered ring;^[8] we started with the simplest substrate, compound **13b**. While the early Grubbs' ruthenium catalyst^[9] failed to induce ring closure within this substrate, our ambition in this regard was realized when diolefin **13b** was subjected to the newest Grubbs^[10] catalyst, **IV** (20 mol%, Scheme 5) in dichloromethane at reflux, conditions that afforded a single macrocyclic product (**14**, Scheme 5A) in 60% yield. X-Ray crystallographic analysis^[11] of **14** (see ORTEP representation) revealed its complete structure, including the *Z* configuration of the $\Delta^{16,17}$ double bond and the arrangement of the enol within the tricarbonyl subunit. Having established the viability of macrocycle formation by olefin metathesis, we then proceeded to investigate the simplest bisalkylated substrate, **13d** (Scheme 5B),



Scheme 5. A) Forging a *Z*-configured 11-membered ring by an olefin metathesis reaction involving disubstituted and trisubstituted double bonds. B) Selective formation of a spirocyclic product from triolefin **13d**. a) cat. **IV** (0.2 equiv), CH₂Cl₂, 40 °C, 5 h, 60% for **13b**; cat. **IV** (0.3 equiv), CH₂Cl₂, 40 °C, 18 h, 30% for **13c**; b) cat. **IV** (0.1 equiv), CH₂Cl₂, 40 °C, 1 h, 85%. Cy = cyclohexyl; Ph = phenyl.

as a substrate for this ring-closing reaction. As we had feared, when this compound was treated with catalyst **IV** (10 mol%), it was rapidly converted to spirocyclic **15** in 85% yield as shown in Scheme 5B. The formation of **15** provoked us to increase the substitution on the terminal olefin to the *gem*-dimethyl level to relocate the metathesis initiation site to the less substituted olefin appended to the aromatic portion of the molecule. We, therefore, subjected substrate **13c** (Scheme 5A) to the same catalyst (**IV**, 30 mol%) and remarkably once again, observed the formation of macrocycle **14**, albeit in reduced yield (30%).

While these results served as a proof of principle for our initial premise that ring-closing metathesis would be a powerful tool to forge the challenging macrocycle of the coleophomones, the tricarbonyl substrates employed left much to be desired in terms of stability and ease of manipulation. To improve upon these two aspects of the sequence we moved to protect the troublesome tricarbonyl moiety, only to discover that the new substrates harbored additional advantages. Thus, exposure of **13a** to excess diazomethane in diethyl ether resulted in the formation of the vinylogous methyl esters **16a**, which precipitated out from the reaction mixture in 48% yield, and **16b**, which could be isolated from the remaining solution in 48% yield (Scheme 6). The latter compound (**16b**) was alkylated with prenyl bromide, after enolate generation with LiHMDS and HMPA, to afford alkylated product **17** (63%) as a 1:1 mixture of geometrical isomers ($\Delta^{8,9}$), each of which existed as a 1:1 pair of atropisomers as revealed by ¹H



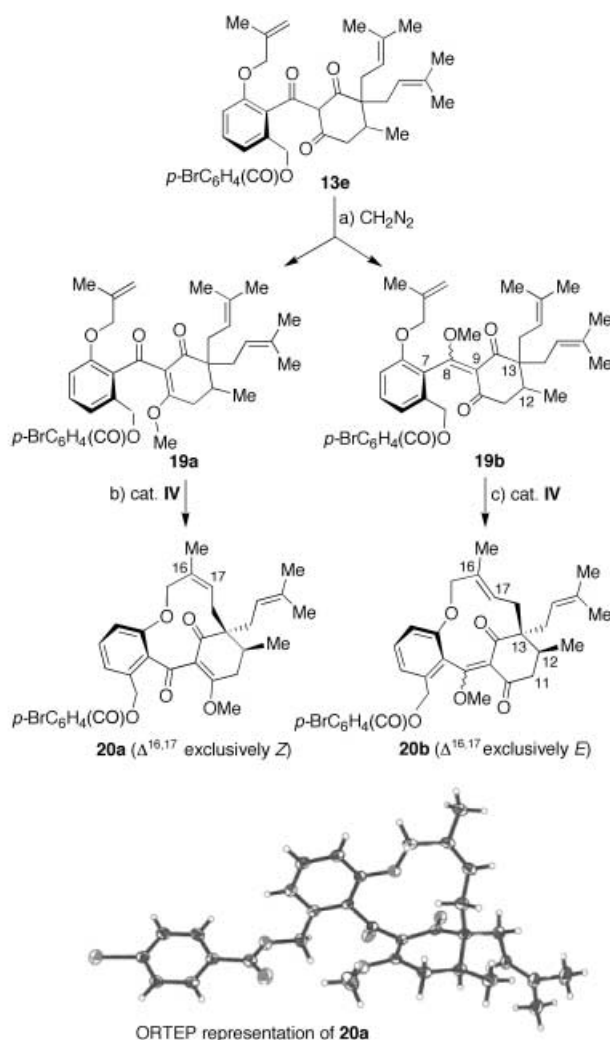
Scheme 6. Protection of the tricarbonyl moiety and reversal of the geometrical outcome of the olefin metathesis reaction leading to an (*E*) $\Delta^{16,17}$ containing 11-membered ring. a) Excess CH₂N₂, Et₂O, 0 °C, 30 min, 48% of **16a** plus 48% of **16b**; b) LiHMDS (1.05 equiv), THF, –78 °C, 1 h; then prenyl-Br (2.0 equiv), –78 → 0 °C, 5 h, 63%; c) cat. **IV** (0.2 equiv), CH₂Cl₂, 40 °C, 20 h, 30% of **18** plus 35% recovered starting material **17**.

NMR spectroscopy. When **17** was subjected to the action of Grubbs' catalyst **IV** (20 mol %) in refluxing dichloromethane for 20 h, a single macrocycle (**18**) was isolated, in 30% yield, and proven to be of the *E* configuration at $\Delta^{8,9}$. Under these conditions, a considerable amount (30%) of the starting material (**17**) was recovered and, interestingly, found to be enriched in the *Z* isomer ($\Delta^{8,9}$). The most tantalizing feature elucidated at this juncture was, however, the fact that the macrocyclic double bond ($\Delta^{16,17}$) bore exclusively the *E* configuration (see NOE effects on structure **18**, Scheme 6). We had now unearthed pathways that led us to both diastereoisomers of the coleophomone macrocyclic skeleton in a specific manner.

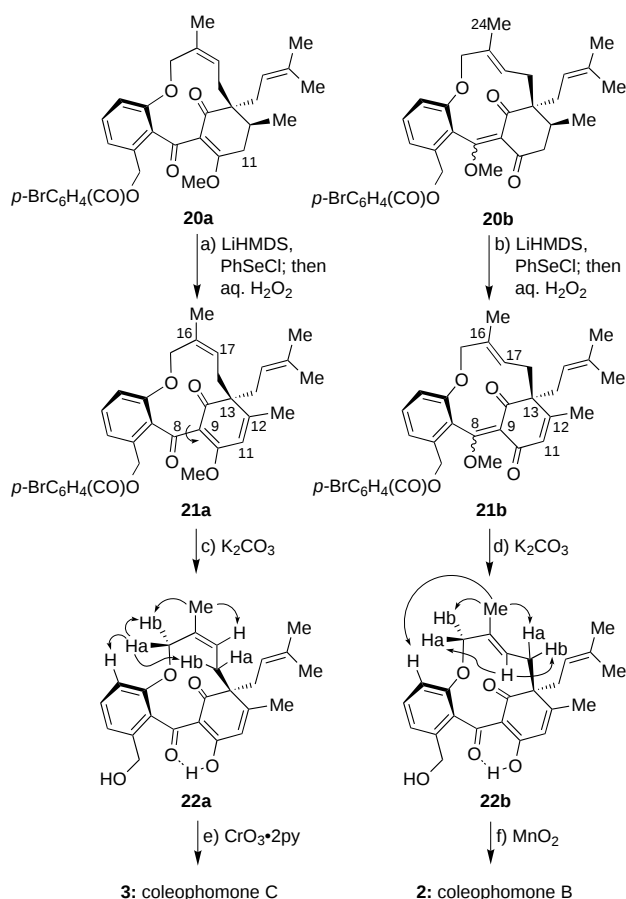
With these results providing the foundation for the next phase, we proceeded to exploit the full potential of our intelligence gathering for the final solution of the coleophomone problem. Thus, fully substituted precursor **13e** (see Scheme 7) was treated with diazomethane under the established conditions and, following flash column chromatography, methoxy derivatives **19a** (32%) and **19b** (48%) were isolated along with a small quantity of the third possible

regioisomer (not shown). As expected, **19a** was a single compound, while **19b** proved to be a mixture of geometrical isomers around the $\Delta^{8,9}$ bond (ca. 1.3:1), each of which again consisted of a pair of atropisomers (ca. 1:1 by ^1H NMR spectroscopy). Upon exposure of the two regioisomers **19a** and **19b**, independently, to the catalyst **IV** (10 mol %) we observed the most pleasing results. Both **19a** and **19b** succumbed to regio- and stereospecific ring-closing metathesis to furnish, in high yields, the corresponding macrocycles **20a** (80%, exclusively *Z*-configured at $\Delta^{16,17}$, ca. 4:1 ratio of atropisomers in CDCl_3 , single atropisomer in CD_3CN) and **20b** (86%, exclusively *E*-configured at $\Delta^{16,17}$, ca. 1:1 *E*:*Z* isomers at $\Delta^{8,9}$). The structures of **20a** and **20b** were established on the basis of nOe studies and, in the former case (**20a**), confirmed by an X-ray crystallographic analysis^[11] (see ORTEP representation). Thus, with exquisite specificity, the olefin metathesis reaction furnishes the two macrocycles processing the opposite configuration at the $\Delta^{16,17}$ bond, each corresponding to a different coleophomone framework. Furthermore, and in contrast to the reaction of the mono-prenylated compound **17** (see Scheme 5), both $\Delta^{8,9}$ diastereoisomers of **19b** reacted smoothly, presumably because the second prenyl group forced the molecule to adopt a more favorable and rigid conformation. The rigidity and, therefore, reduced entropy^[12] of **19a** and **19b** is also presumed to be responsible for the apparent irreversibility of the ring-closing metathesis as evidenced by the absence of any spirocyclopentene products in the reaction mixture and the high yields of the desired macrocycles (**20a** and **20b**). Another fascinating feature of these ring-closing metatheses is their exquisite diastereoselectivity, that is, only the prenyl group occupying the *cis* position to the adjacent methyl group (C12) participates in the reaction. This preference presumably results from the fact that it places the remaining prenyl side chain *trans* to the C12 methyl group, an arrangement that allows both groups to occupy the lower-energy equatorial positions on the cyclohexane ring. Finally, we were able to confirm our earlier hypothesis that the unprotected tricarbonyl system was detrimental to the olefin metathesis reaction by comparing the poor performance (<20% yield of cyclized product) of **13e** (Scheme 7) under the same cyclization conditions with the stellar showing of its protected derivatives **19a** and **19b**.

As a prelude to the final drive toward the coleophomones, the introduction of the $\Delta^{11,12}$ bond was accomplished in both series by a one-pot phenylselenide formation/oxidation/syn-elimination sequence to afford **21a** as a single compound and **21b** as a mixture of geometrical isomers (61 and 53% overall yield, respectively, Scheme 8). This transformation increased the ratio of geometrical isomers ($\Delta^{8,9}$) in **21b** in favor of the *E* isomer (**20b** *E*:*Z* ca. 1:1 $\rightarrow$ **21b** *E*:*Z* ca. 3:1), presumably owing to the apparent steric encumbrance of the C11 methylene group caused by the direct positioning of the C24 methyl group above it in the *Z* isomer (molecular modeling and nOe studies). The recovered starting material **20b** (15%) was enriched in the *Z* isomer. Exposure of **21a** and **21b** to K_2CO_3 in methanol at ambient temperature led to global deprotection and afforded **22a** (90% yield) and **22b** (96% yield), respectively, both as single compounds (see Scheme 8 and Table 1 for spectroscopic data). At this juncture, the



Scheme 7. Stereospecific olefin metathesis reactions leading to (*Z*) and *E* isomers of 11-membered rings en route to the coleophomones. a) Excess CH_2N_2 , Et_2O , 0°C , 1 h, 32% of **19a** plus 48% of **19b**; b) cat. **IV** (0.1 equiv), CH_2Cl_2 , 40°C , 3 h, 80%; c) cat. **IV** (0.1 equiv), CH_2Cl_2 , 40°C , 3 h, 86%.



Scheme 8. Completion of the total synthesis of coleophomones B (2) and C (3). a) LiHMDS (1.3 equiv), THF, $-78 \rightarrow -10^\circ\text{C}$, 1 h; then PhSeCl (1.4 equiv), $-78^\circ\text{C} \rightarrow 20^\circ\text{C}$, 30 min; then sat. NH_4Cl (excess), 31% aq. H_2O_2 (excess), 25°C , 1 h, 61%. b) LiHMDS (1.3 equiv), THF, $-78 \rightarrow 25^\circ\text{C}$, 1 h; then PhSeCl (1.4 equiv), $-60 \rightarrow 25^\circ\text{C}$, 30 min; then sat. NH_4Cl (excess), 31% aq. H_2O_2 (excess), 25°C , 1 h, 53%, plus 15% recovered 20b; c) K_2CO_3 (3.0 equiv), MeOH, 25°C , 3 h; then H_2O (excess), 24 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 , $0 \rightarrow 25^\circ\text{C}$, 20 min; then 22a, 25°C , 2 h, 81%; f) MnO_2 (20 equiv), Et_2O , 36°C , 8 h, 73%. py = pyridine.

coalescence to a single isomer in each series allowed additional and unequivocal confirmation of our earlier distinction between *Z/E* isomerism and atropisomerism by using nOe studies (see structures 22a and 22b, Scheme 8). Oxidation of 22b with MnO_2 in diethyl ether produced, cleanly^[13] and in 73% yield, coleophomone B (2) whose spectroscopic data matched those of the natural product.^[1,2] Likewise, coleophomone C (3) was accessed by oxidation of 22a, this time with Collins' reagent (this isomer reacts sluggishly with MnO_2) in 81% yield and, once again, the spectroscopic data of the synthetic sample proved to be identical to those of an authentic sample.^[1] Despite the reported equilibrium^[2] between 1 and 2 we choose to refrain from declaring a formal total synthesis of coleophomone A (1) pending further experimentation.

In conclusion we have developed an expedient and stereocontrolled total synthesis of coleophomones B (2) and C (3) through an initially convergent route that diverges at a late stage to allow stereospecific construction of the highly

Table 1. Selected data for compounds 22a and 22b.

22a: yellow oil; $R_f = 0.44$ (silica gel, hexane/EtOAc, 1/1); IR (film): $\tilde{\nu}_{\text{max}} = 3436, 2920, 1651, 1549, 1449, 1261, 1008, 914, 726 \text{ cm}^{-1}$; ^1H NMR (600 MHz, CDCl_3): $\delta = 15.71$ (s, 1H), 7.38 (t, $J = 7.7 \text{ Hz}$, 1H), 7.11 (d, $J = 7.7 \text{ Hz}$, 1H), 6.89 (d, $J = 7.7 \text{ Hz}$, 1H), 6.29 (s, 1H), 5.28 (dd, $J = 11.0, 6.6 \text{ Hz}$, 1H), 4.56 (d, $J = 12.1 \text{ Hz}$, 1H), 4.51 (d, $J = 12.1 \text{ Hz}$, 1H), 4.50 (br dd, $J = 6.5, 5.5 \text{ Hz}$, 1H), 4.34 (d, $J = 8.7 \text{ Hz}$, 1H), 4.10 (d, $J = 8.7 \text{ Hz}$, 1H), 2.84 (dd, $J = 14.8, 6.0 \text{ Hz}$, 1H), 2.69 (dd, $J = 14.3, 11.0 \text{ Hz}$, 1H), 2.22 (m, 2H), 2.08 (s, 3H), 1.82 (s, 3H), 1.55 (s, 3H), 1.50 ppm (s, 3H); ^{13}C NMR (150 MHz, CDCl_3): $\delta = 198.8, 181.0, 164.1, 156.4, 139.8, 136.0, 134.4, 131.9, 131.7, 131.4, 124.1, 123.6, 122.2, 117.8, 115.1, 113.1, 69.7, 64.2, 59.2, 39.0, 37.1, 25.7, 23.2, 20.1, 18.1 \text{ ppm}$; HRMS (MALDI): calcd for $\text{C}_{25}\text{H}_{27}\text{O}_4$ [$\text{MH} - \text{H}_2\text{O}$]: 391.1904; found: 391.1905; MS (ESI): 409 [MH^+], 431 [MNa^+]

22b: amorphous solid; $R_f = 0.32$ (silica gel, hexane/EtOAc, 1/1); IR (film): $\tilde{\nu}_{\text{max}} = 3412, 2920, 1651, 1556, 1455, 1262, 997, 866, 736 \text{ cm}^{-1}$; ^1H NMR (500 MHz, CDCl_3): $\delta = 16.54$ (s, 1H), 7.29 (t, $J = 8.2 \text{ Hz}$, 1H), 7.12 (d, $J = 8.2 \text{ Hz}$, 1H), 7.09 (d, $J = 7.4 \text{ Hz}$, 1H), 6.38 (s, 1H), 5.41 (br d, $J = 12.0 \text{ Hz}$, 1H), 4.66 (d, $J = 12.3 \text{ Hz}$, 1H), 4.56 (d, $J = 11.4 \text{ Hz}$, 1H), 4.55 (br dd, $J = 7.4, 5.5 \text{ Hz}$, 1H), 4.49 (d, $J = 12.3 \text{ Hz}$, 1H), 4.31 (d, $J = 11.4 \text{ Hz}$, 1H), 2.99 (dd, $J = 14.2, 6.8 \text{ Hz}$, 1H), 2.44 (t, $J = 12.8 \text{ Hz}$, 1H), 2.33 (br d, $J = 13.8 \text{ Hz}$, 1H), 2.25 (dd, $J = 14.6, 6.4 \text{ Hz}$, 1H), 2.11 (s, 3H), 1.58 (br s, 3H), 1.57 (br s, 3H), 1.23 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 200.0, 198.6, 183.0, 164.9, 153.5, 139.6, 135.7, 134.9, 132.2, 129.6, 128.1, 123.3, 122.9, 118.3, 118.0, 114.2, 76.3, 63.7, 58.8, 38.3, 34.4, 25.7, 20.1, 19.7, 18.0 \text{ ppm}$; HRMS (MALDI): calcd for $\text{C}_{25}\text{H}_{27}\text{O}_4$ [$\text{MH} - \text{H}_2\text{O}$]: 391.1904; found: 391.1898; MS (ESI): 409 [MH^+], 431 [MNa^+]

strained and synthetically challenging macrocyclic scaffolds associated with these molecules via an olefin metathesis reaction. This unprecedented accomplishment bodes well for this venerable reaction that is becoming increasingly enabling for organic synthesis through the discovery of new catalysts to initiate it and the design of novel strategies to apply it.

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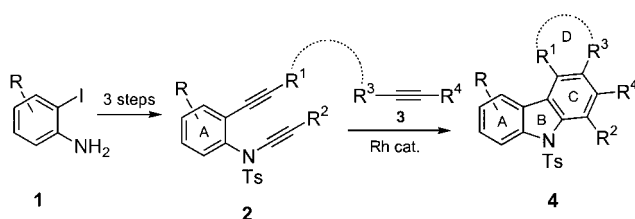
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A Highly Efficient and Flexible Synthesis of Substituted Carbazoles by Rhodium-Catalyzed Inter- and Intramolecular Alkyne Cyclotrimerizations**

Bernhard Witulski* and Carole Alayrac

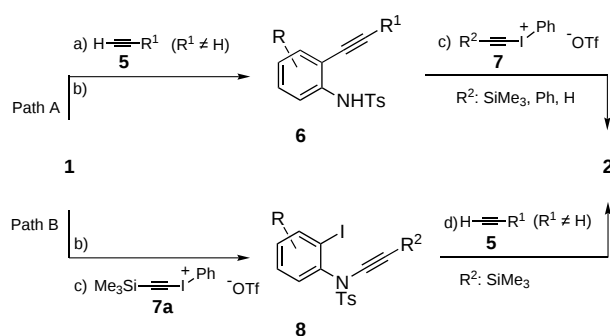
Syntheses of substituted carbazoles have attracted considerable attention because carbazole alkaloids are a growing class of natural products that exhibit a variety of biological activities.^[1,2] Moreover, annelated carbazoles structurally related to the natural indolocarbazole staurosporine have gained significance because of their protein kinase C (PKC) and topoisomerase inhibitory activity.^[3]

Although several syntheses of substituted carbazoles as well as chemical modifications of the carbazole nucleus are established,^[1,4] the major challenge in carbazole chemistry arises from the question of how to functionalize regioselectively up to eight aromatic ring positions. We have designed a strategy for the assembly of the carbazole nucleus by an A→ABC or A→ABCD ring-formation approach that is based on the reliability of the Sonogashira reaction,^[5] our previously reported synthesis of functionalized ynamides,^[6] and the efficiency of transition-metal-catalyzed alkyne cyclotrimerizations (Scheme 1).^[7]



Scheme 1. A→ABC or A→ABCD ring-formation approach to substituted carbazoles by rhodium-catalyzed alkyne cyclotrimerization.

The diynes **2** were prepared in three steps starting from readily available 2-iodoanilines **1**. Sonogashira reactions between **1** and terminal alkynes **5** followed by N-tosylation of the aniline functionality gave alkynes **6**, which thereafter underwent N-ethynylation with alkynylidonium salts **7** to give the diynes **2** in good overall yields (Scheme 2, path A).



Scheme 2. a) **5** (1.3 equiv), 5 mol % $[\text{PdCl}_2(\text{PPh}_3)_2]$, 10 mol % CuI, NEt_3 , DMF, room temperature, 60–98%; b) TsCl, pyridine, THF, 70–92%; c) potassium hexamethyldisilazane (KHMDs), toluene, 0°C, then addition of **7** (1.4 equiv), room temperature, 52–93% for **6**→**2**, 87–98% for **8**; d) **5** (1.4 equiv), 5 mol % $[\text{PdCl}_2(\text{PPh}_3)_2]$, 10 mol % CuI, 10 mol % PPh_3 , NEt_3 , DMF, 80°C, 54–68%.

Alternatively, N-ethynylation reactions with **7a** were carried out with tosylated **1** to give the ynamides **8**, which were then converted to **2** through Sonogashira reactions (Scheme 2, path B). While the conversion of **1** to **6** proceeded readily at room temperature, cross-coupling reactions with **8** to give **2** required heating to 80°C, probably because of an increase of steric hindrance. Notably, the use of trimethylsilylacetylene in the Sonogashira reaction, or the use of **7a** for the N-ethynylation reaction following either path A or B in Scheme 2 allowed further manipulations of the diynes **2** through protective group strategies.

Crossed alkyne cyclotrimerizations between diynes **2** and monoalkynes **3** promoted by Wilkinson's catalyst^[6b,8] proceeded under very mild conditions (3–5 mol % $[\text{RhCl}(\text{PPh}_3)_3]$, 5–6 equivalents of **3**, toluene as solvent) to give the carbazoles **4** in high yields (Scheme 1, Table 1). Notably, the additional triple bond in **2e** did not interfere with the formation of carbazole **4e** (80% yield, Table 1, entry 5). The outstanding efficiency of the carbazole formation by crossed alkyne cyclotrimerizations is presumably a consequence of conformational restrictions present in the diynes **2**. A conformation in which both alkyne moieties are close to each other appears likely and therefore favors the overall catalytic process.

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