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Kilogram-Scale Production of Corannulene

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Supporting Information

ABSTRACT: An efficient entry process for the synthesis of corannulene has been demonstrated on kilogram scale. Compared to the discovery and gram-scale syntheses, the amounts of solvents and reagents per gram of product were greatly reduced. Priority was given to implement the least toxic agents possible. Improvements in the purification of products obviated the need for column chromatography, alleviating four chromatographic operations. A new reduction method for the final step of the synthesis decreased reaction time from 6 to 0.5 days, and avoided the use of 100 equiv of zinc metal. The process now comprises nine steps, each of which runs smoothly at 100-L scale with a charging of 3−12 kg of educt. A total of 1.3 kg corannulene was isolated. This kilogram-scale process reduces material costs by over 2 orders of magnitude compared to that for the published gram-scale syntheses. Key opportunities in the process are identified for further improvements that should make synthesis on 100-kg scale feasible with a target price for **1** that is suitable for commercial production and engineering application.

INTRODUCTION

Comprising 20 carbon atoms, corannulene (**1**) is one-third the size of C_{60} and the smallest subunit of the buckyball motif that still maintains a curved surface.[1] The curvature of **1** and C_{60} give both compounds unique electronic properties that are not observed in planar polyaromatic hydrocarbon (PAH) analogues such as pyrene or naphthalene.[2] The literature around corannulene abounds with a wide diversity of mono- and multifunctionalized derivatives.[3] These derivatives serve as precursors for numerous classes of materials, such as graphitic tubes/caps,[4] liquid crystals,[5] dendrimers,[6] polymers,[7,8] cruciforms,[9] cyclophanes,[10] and molecular clefts.[11] Despite the ever-growing academic interest in **1**, the need for a substantial synthetic commitment to prepare **1** and derivatives creates a barrier to broad materials and engineering applications. Thus, a "sustainable" synthesis on scale would go a long way toward allowing corannulene to grow beyond being an esoteric molecule of academic interest to an industrially interesting prospect, with direct application in materials chemistry. Herein, the optimization and kilogram production of corannulene intends to provoke a commercially viable production.

HISTORICAL DEVELOPMENT

Approaching half a century ago, Lawton and Barth reported the first synthesis of corannulene in 17 linear steps (<1% overall yield) starting from acenaphthene (Scheme 1).[1] Their strategy builds the structure up ring by ring and introduces strain as late as possible in the synthesis by trading the stabilization from aromatization of the rings for the destabilization of the strain due to out-of-plane distortion. Albeit a pioneering *tour de force*, the lengthy synthesis and low overall yield of **1** could not stimulate a wave of exploration in corannulene chemistry. That would have to wait for a new, more tractable synthesis.

From 1970 to 1990, several groups attempted to find alternative routes to corannulene. A basic Friedel−Crafts strategy[12] looked attractive but went fallow. Creation of naphthyl-phenyl cyclophanes as precursors to corannulene also never bore fruit.[13] In the glory of hindsight and physical organic chemical analysis, both these unsuccessful approaches underestimated the strain needed to reach the transition state en route to the final closure, and overestimated the aromatic stabilization benefit one might obtain from creating the corannulene unit. Indeed, higher-energy reaction conditions or higher-energy synthetic precursors would be needed to bring a new synthesis to fruition.

In the early 1990s two new synthetic strategies to **1** appeared. Both chose a bilaterally symmetric retrosynthetic strategy over the ring-by-ring methods; however, these retrosynthetic approaches differed in their choice of which bond type of **1** to disconnect: (a) flanking or (b) rim (Figure 1). The former leads to a relatively low energy and unstrained 7,10-disubstituted fluoranthene, in contrast to the latter, which foresees a sterically crowded 1,6,7,10-tetrasubstituted fluoranthene. Disconnection (a) had been an unsuccessful strategy when coupled to Friedel−Crafts chemistry in the forward direction. Disconnection (b) resembles the ultimate stage of the classic Lawton-and-Barth strategy, wherein acyloin chemistry enabled a successful synthesis.

The failure of disconnection (a) when coupled to Friedel−Crafts chemistry can be seen in the additional strain needed to obtain the transition state to attack on the pi face. The molecule must fold to a deeper-bowled and higher-strained conformation before bond formation can occur. Also the reaction conditions are prone to rearrangements that would allow for back reaction to ring-opened products. Disconnection (b) requires a higher-energy synthetic precursor; however, in combination with a reductive, radical, or insertion reaction, wherein the transition state to carbon−carbon bond formation can be reached by a more or less linear least-motion path of the proximal units, this approach could be much more tractable. The experience of Lawton and Barth with the acyloin reaction empirically supports this analysis.

Larry Scott's and our laboratories independently developed the two pathways simultaneously. The first strategy, from Scott and co-workers,[14] applied high-temperature, gas-phase flash

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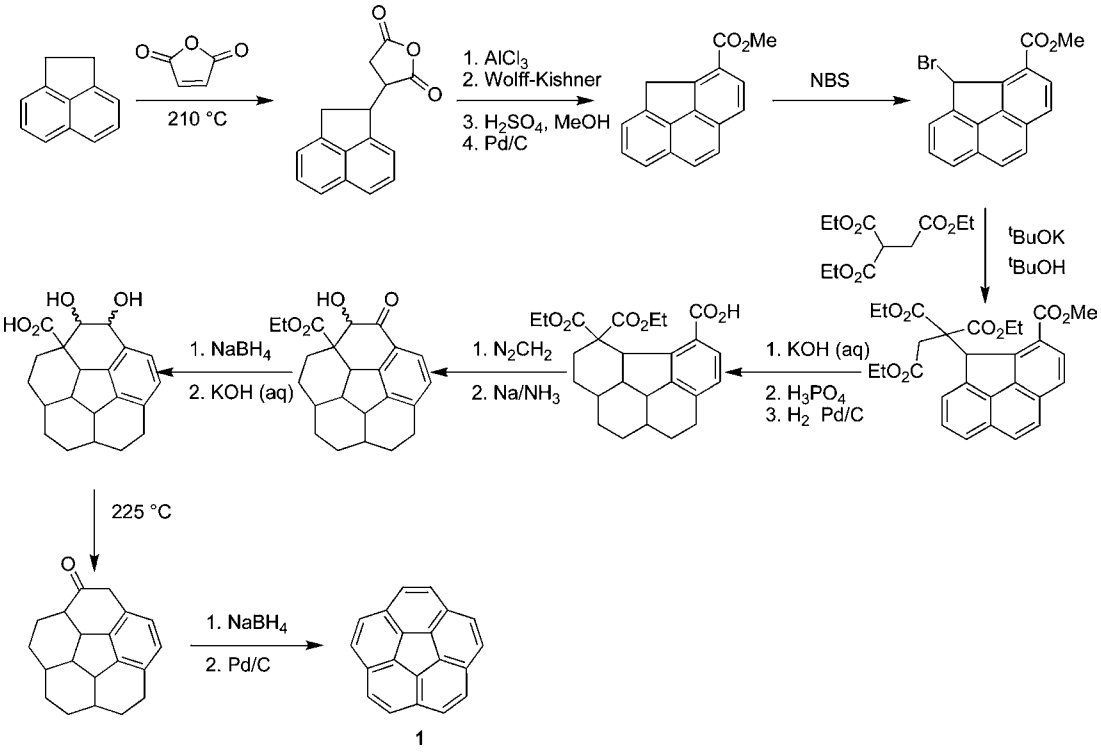
Scheme 1. First synthesis of corannulene 1



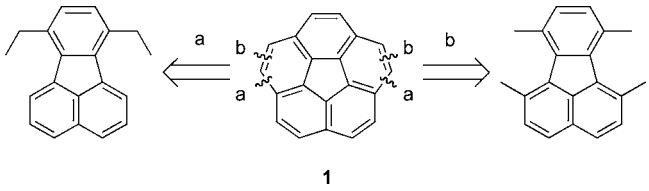


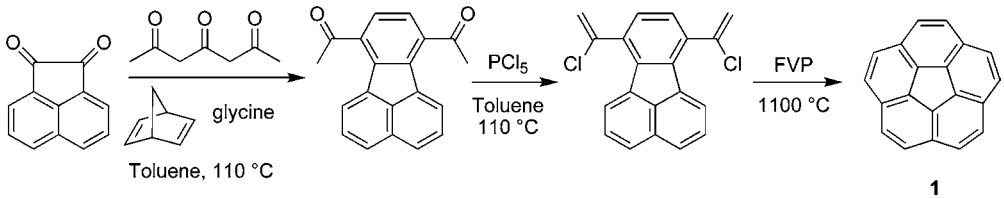
Figure 1. Different retrosynthetic approaches to **1**. Disconnection between the flanking (a) or rim (b) carbons of **1** results in two different fluoranthene precursors.

vacuum pyrolysis (FVP) to achieve high reaction energies for short residence times. The idea that these conditions could result in effective ring closure came from the pioneering work of R. F. C. Brown, in which he showed that under FVP conditions acetylenes could isomerize and react as vinylenes.[15] The high energy of the reaction conditions opened a reaction path not available by conventional chemical methods.

The optimized version of the procedure sets out from the chlorovinyl compound (Scheme 2), instead of the acetylene originally foreseen from the Brown chemistry. Corannulene was produced on gram-scale in a 20−25% yield starting with commercially available acenaphthenequinone. Although this route succeeded in a small number of steps, it suffered from the following: modest yields, poor to no functional group tolerance, limited possibility for scale-up and undesired thermal rearrangements/side products.

The second strategy, pioneered in our group, used milder and more selective solution phase chemistry to achieve the synthesis of corannulene. The initial solution phase synthesis (Scheme 3) follows the precedent of Buu-Hoi set back in 1942.[16] It starts by preparing 2,7-dimethylnaphthalene (**4**) by the addition of the Grignard of (**2**) to 4,4-dimethoxy-2-butanone followed by acidic workup leading to deprotection and ring closure.[17] Chloromethylation of **4** occurs regioselectively at the 1 position, and homologation with KCN and hydrolysis in sulfuric acid/water leads to the acetic acid derivative. Formation of the acid chloride and Friedel−Crafts ring closure produces 2,7-dimethylacenaphthone, which is converted to the analogous acenaphthaquinone (**5**) by selenium dioxide oxidation.[18] The crossed-aldol condensation of **5** with 3-pentanone and subsequent Diels−Alder addition yielded 1,6,7,10-tetramethylfluoranthene (**7**), which by Wohl−Ziegler radical bromination was converted to 1,6,7,10-tetrakis-(bromomethyl)fluoranthene (**8a**). The bridging thioether was prepared by nucleophilic displacement with sodium sulfide, from which sulfur extrusion and aromatization led to **1**. This expensive and lengthy synthesis proved the principle of the bilaterally symmetric approach[8a] but lacked the practicality of anything close to a scalable synthesis. Toxic reagents like

Scheme 2. Flash vacuum pyrolysis method developed by Scott



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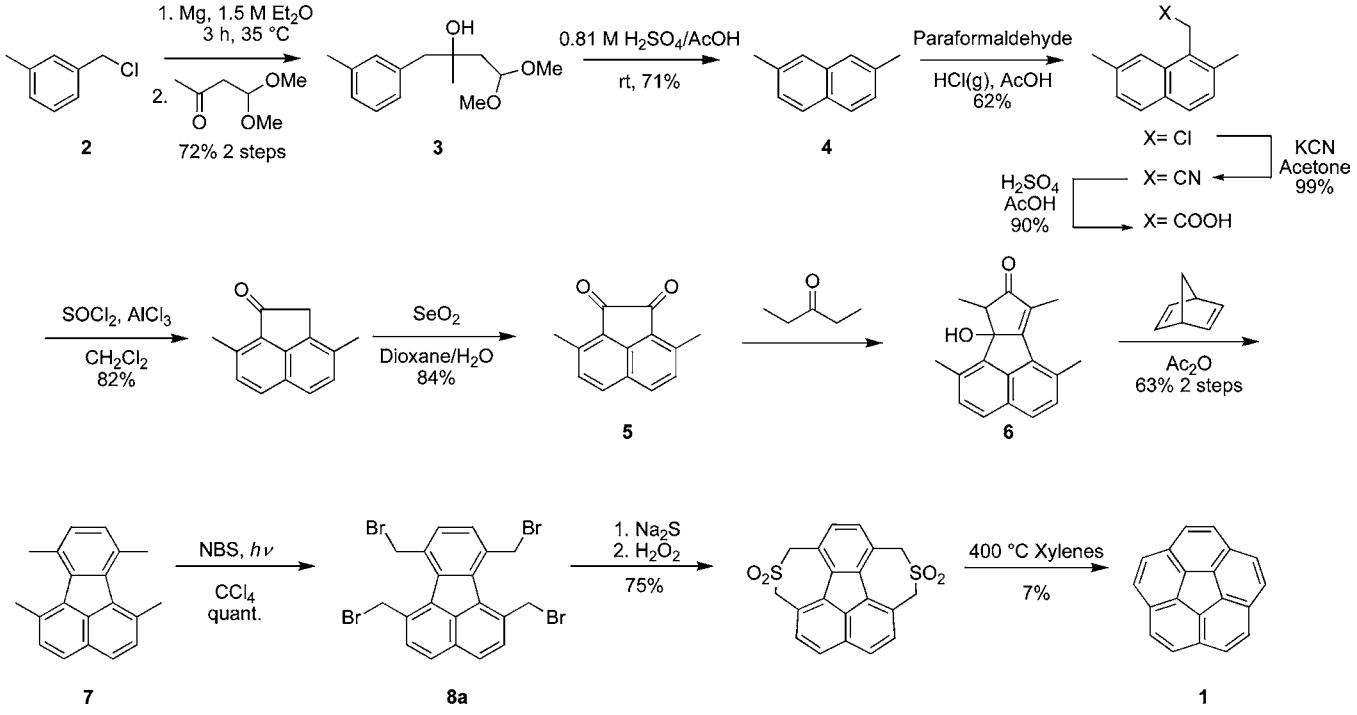
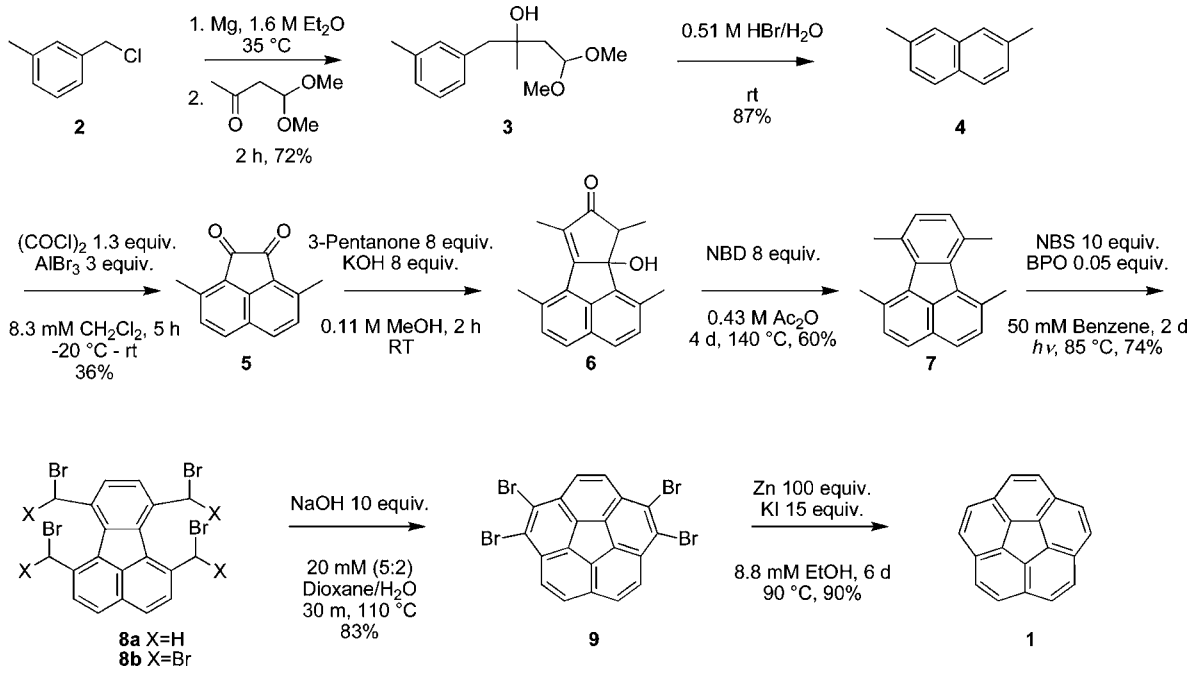
Scheme 3. First corannulene synthesis by the Siegel group



Scheme 4. Solution phase synthesis of corannulene (2006)



selenium dioxide further weakened the practical aspects of this synthesis.

Further investigations lead to the implementation of a direct formation of **5** from **4** by Friedel–Crafts acylation with oxalyl chloride (Scheme 4). The method yielded two closely related isomers of dimethylacenaphthaquinone, which required stringent chromatographic separation; however, it obviated many steps and the use of selenium dioxide. Benzylic bromination of **7** could be pushed to give the octabromide **8b**, which afforded a ring closure of the flanking bonds by using low valent titanium or vanadium, eliminating the need for pyrolysis.[10,19] Here the first gram scale solution phase synthesis of corannulene was established and shown to produce not only the basic core but also specific derivatives.

Investigations toward the formation of the tetracarboxaldehdyde cognate of **7** or **8b** led Sygula and Rabideau to attempt hydrolysis of **8b**.[20] Serendipitiously, hydrolysis did not lead to the expected precursor but instead deprotonated the remaining benzylic hydrogen and initiated carbon–carbon bond formation, leading to tetrabromocorannulene (**9**). This reaction was strategically important and offered certain advantages for gram-scale syntheses; however, the use of dioxane and the low

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Table 1. Comparison of reagents required before (2006) and after (2011) for the synthesis of 3 to produce 1 kg of corannulene[22]

	2006		2011	
	reagent	kg	reagent	kg
reaction:	**2**	8.0	**2**	7.7
	diethyl ether	41	diethyl ether	40
	magnesium	1.7	magnesium	1.6
	dimethoxybutanone	7.0	dimethoxybutanone	6.3
workup:	water	59	water	77
	NH_4Cl solution	55	NH_4Cl solution	27
	$MgSO_4$	5.7	Na_2SO_4	3.8
			MTBE	110
purification:	N/A		N/A	
yield[23]:	72% (**3**)	9.2	85% (**3**)	9.2
vol. yield:	reaction: 16%	total: 5.1%	reaction: 16%	total: 3.0%
E-factor[24]:		17		28

Table 2. Comparison of reagents required before (2006) and after (2011) for the synthesis of 4 to produce 1 kg of corannulene[22]

	2006		2011	
	reagent	kg	reagent	kg
reaction:	**3**	9.2	**3**	9.3
	AcOH	39	AcOH	45
	HBr (48%)	44	H_2SO_4 (97%)	5.6
	Water	94	water	78
workup:			$MgSO_4$	3.1
			toluene	70
			Na_2CO_3	2.3
			sat. NaCl solution	0.43
purification:	N/A		ethanol	19
yield[23]:	87% (**4**)	5.2	71% (**4**)	4.3
vol. yield:	reaction: 7.8%	total: 3.2%	reaction: 9.4%	total: 1.9%
E-factor[24]:		34		52

volume yield of the reaction made this operation very costly and not very "green" if contemplated for synthesis on multi-kilogram scale.

Reduction of **9** was possible using ~100 equiv of zinc and potassium iodide in ethanol. Alternatives using lithium aluminum hydride had also been reported. The excessive waste of the former and harsh reagents of the latter also required attention for a successful scale-up.

Such was the state of the art in corannulene synthesis when the present investigation in scale-up began; eight steps (overall yield 7.4%), four chromatographic separations (compounds **5**, **7**, **8b**, and **1**), several undesirable solvents, harsh or excessive reagent and no step-volume yield above 3%. To produce 120 g of corannulene required almost a metric ton of solvent.

Four general challenges were the focus of this initial optimization: (1) Reduce or replace as many costly or toxic reagents as possible; (2) Increase the volume yields toward a target of 10% from values in some cases below 1%; (3) Enhance the robustness throughout the synthesis by mechanistic insight and testing of critical parameters; (4) Remove all chromatographic separations, including that needed to separate the physically similar isomers of dimethylacenaphthenequinone.

RESULTS AND DISCUSSION

Synthesis of 2,7-Dimethylnaphthalene (4). Conversion of α-chloro-*m*-xylene (**2**) to 2,7-dimethylnaphthalene (**4**) was accomplished through a Grignard addition of dimethoxybutanone followed by acidic ring closure. The production of **3** closely followed the reported procedure[17] and required minimal optimization (Table 1). Important in this step were the safety considerations associated with a Grignard reaction.[21] Diethyl ether is not a preferred solvent on scale due to its extremely volatile and flammable nature. Attempts to use tetrahydrofuran in this step led to substantial amounts of 1,2-bis-(3-methylphenyl)ethane, the product of homocoupling of the Grignard reagent. Methyltetrahydrofuran and methyl *tert*-butylether were not investigated. Suppression of the coupling reaction in other solvents would not allow the replacement of diethylether in this step. Fortunately, it was found that with incremental scale-up of this step and close monitoring of the reaction, production was possible without problems.

For the ring closure of **3** to yield 2,7-dimethylnaphthalene the original paper reported using a 0.51 M mixture of glacial acetic acid and 48% hydrobromic acid. During production, 95% sulfuric acid replaced the hydrobromic acid (Table 2) and a higher concentration of 0.81 M H_2SO_4 in acetic acid was achieved. Crystallization resulted in a 71% yield of **4**, lower than the literature yield of 87%. Two additional side products were isolated and characterized, 2,5-dimethylnaphthalene and 1,2-bis-(3-methylphenyl)ethane, accounting for 7% and 6% yields respectively.

Acylation of Dimethylnaphthalene (4) to Acenaphthenequinone (5). The Friedel–Crafts acylation of **4** with oxalyl chloride presented several problems. The initial synthesis[25] used large excess of reagents like aluminum bromide and oxalyl chloride in dichloromethane to yield a mixture of primarily two isomers, **5** and **5b** in a 55–60% combined yield. The ratio of isomers ranged from 1:1 to 3:1 in favor of **5**. Separation of these isomers was possible by column chromatography, but required large amounts of ethyl acetate/hexane and a silica gel-to-product ratios of 150:1 because both isomers have similar elution times. Furthermore, the reaction was not robust and yields could vary by as much as 50%.

The systematic optimization of **5** began by screening a series of Lewis acids in a variety of solvents. The initial screen of Lewis acids included $AlBr_3$, $AlCl_3$, $SnCl_4$, and $BF_3(C_2H_5)_2O$ in dichloromethane. Aluminum bromide showed the best reactivity in dichloromethane. A wider screening of solvents was done for each of the four Lewis acids. The solvents tested included toluene, chlorobenzene, THF, hexane and cyclohexane. The reactions were started at temperatures between −30 and −10 °C then, if no consumption of starting material could be detected by GC–MS using an internal standard of octadecane, were slowly heated to 20–25 °C. The result of the initial screening showed that of the Lewis acids tested, only $AlBr_3$ and $AlCl_3$ showed any reactivity towards the acylation, regardless of temperature, solvent or time.

Next, the $AlCl_3$ was screened against a wider variety of solvents including those previously mentioned as well as nitrobenzene, 1,2-dichlorobenzene and CS_2. Again, the initial temperature ranged between −30 and −20 °C then was slowly raised to −10 to 0 °C. The reactions showed consumption of the starting material but a poor yield of <25% of **5**. Upon interpretation of the side products we speculated that the Lewis acid was reactive enough to allow for the first acylation at low

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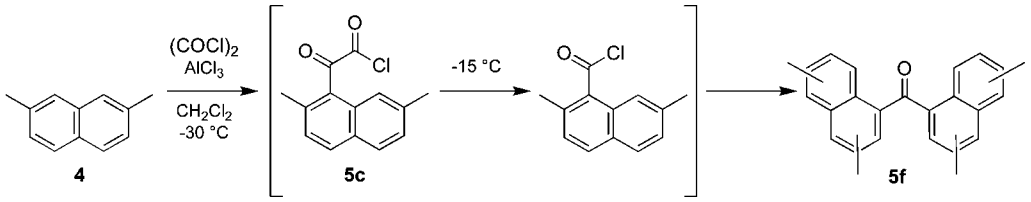
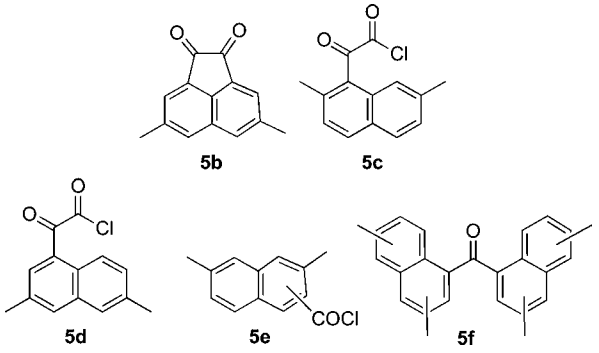
Scheme 5. Decomposition of the monoacylated intermediate 5c



temperatures but required increased temperatures to overcome the energy barrier for the second acylation. Reported literature[26] supported this theory and showed that increasing the temperature to even 0 °C will cause decomposition in such a molecule, which was evident in our reaction by the formation of **5f** as shown in Scheme 5.

Other proposed side products of this reaction were determined by mass analysis and NMR spectroscopy (**5b**–**f**).



Although aluminum chloride alone did not furnish comparable yields, we anticipated that a mixture of the two Lewis acids could be successful. Per mole, aluminum chloride costs about 1/20th the price of aluminum bromide at present.[27] The ratio of the Lewis acids was varied from 100:0 to 0:100 $AlBr_3$:$AlCl_3$ (Table 3).

Table 3. Friedel–Crafts acylation using mixture of $AlBr_3$ and $AlCl_3$

lewis acid (%)		major products[a](%)		
$AlBr_3$	$AlCl_3$	**4**	**5**	**5b**
100	0	5	38	20
75	25	5	31	16
50	50	2	30	13
25	75	2	19	6
0	100	4	15	4

[a]All reactions were performed on 500 mg scale using 1.2 equiv oxalyl chloride and 2.6 equiv Lewis acid in dichloromethane. A temperature ramp of −40 to −15 °C over 4 h was applied. Percentages of products were determined by GC–MS using an internal standard of octadecane.

The screening results of the $AlBr_3$/$AlCl_3$ mixtures in dichloromethane suggested that replacement of aluminum bromide with aluminum chloride lowers the reaction yield more than an acceptable amount. A 1:1 mixture of $AlBr_3$/$AlCl_3$ using hexane at 40 °C showed a 29% yield of **5** but almost no **5b** (98:2). These conditions were important because, if an efficient separation method for **5** and **5b** could not be achieved, then selectively synthesizing only **5** might have been the best strategy for obtaining pure product on scale. Another highlight of this step was the replacement of 50% of the $AlBr_3$ with the cheaper aluminum chloride. The disadvantages to this step were that hexane is an undesirable solvent due to its electrostatic discharge and its neurological toxicity.[28] Also, the aluminum chloride does not completely dissolve and the mixture of oxalyl chloride and **4** in hexane must be added at temperatures in excess of 40 °C to keep **4** from crystallizing. Replacing hexane with heptane addressed the safety considerations but by doing so also resulted in a lower yield for **5**. The downfalls of this reaction just described were problematic enough that these conditions were thought to be a last resort and aluminum bromide in dichloromethane was considered the best option for moving further. Continued optimization of these conditions and efficient separation of the isomers **5** and **5b** were studied in parallel.

A reaction profile was performed on 10-g scale with an in-process control via HPLC every 30 min. The first reaction with both Lewis acids present in an equal molar ratio (Figure 2)

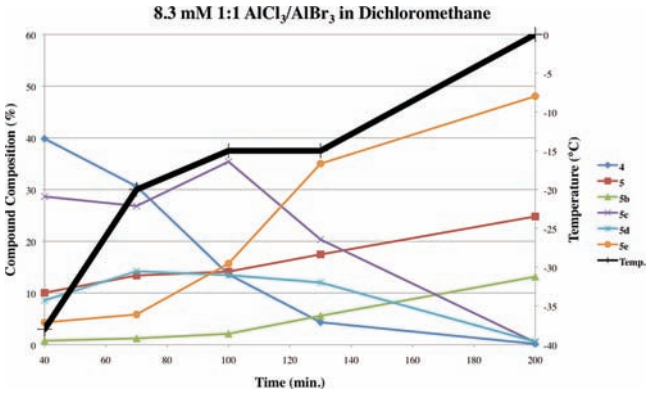


Figure 2. In process control of **4**, **5** and **5b**–**5e** composition (HPLC) along time/temp profile.

resulted in a 25% yield of **5**, as much of it decomposed to **5e** (48%).

We hypothesized that as previous research showed aluminum chloride to be suitable for the first acylation, aluminum bromide could be added later in the reaction to promote the second acylation. This delayed addition of $AlBr_3$ would reduce the amount of aluminum bromide needed while maintaining the yield of **5**. Surprisingly in the presence of only $AlCl_3$, after two hours more than 50% of the detected intermediate was **5c**, the precursor to **5**. However, upon addition of $AlBr_3$, most of **5c** was either converted to **5b** or decomposed to **5e**. Although it is still not fully understood why the addition of aluminum bromide caused the formation of side products and not the desired diketone **5**, the results were reproducible and in end favored the formation of **5b** over **5** in a 4:1 ratio. A stability test of **5** was performed and no decomposition was detected in the

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presence of aluminum bromide and aluminum chloride over a temperature range of −40 to 25 °C.

Finally, it was decided to use only $AlBr_3$. The concentration and stoichiometry of reagents were varied to determine that the optimal molarity of 0.23 M of **4** in dichloromethane (Table 4) resulted in a reproducible combined yield of 73% (2:1) of **5** and **5b** (Figure 3) when a temperature gradient of −38 to −15 °C over 6 h was applied, as shown in Scheme 6.

Having accepted a 2:1 mixture of **5** and **5b** as the best synthetic outcome, the focus shifted to developing an efficient method for isolation and purification of the product. Chromatography was not seen as an option. Both isomers have very similar physical properties; their solubilities were not substantially different in a broad spectrum of solvents.[30] The key chemical difference is the steric environment in the plane of the quinone function. Normal kinetic attack on carbonyls occurs via Burgi−Dunitz[31] approaches out of the carbonyl plane, therefore such strategies seemed unlikely to help, and screening revealed no exception to this expectation. Imine formation would occur under thermodynamic control and would place a new substituent in the plane, where the largest steric difference between the isomers could be exploited. Such a process showed greater mechanistic promise and indeed imine formation proceeds for **5b** better than **5**. More importantly, amino acid hydrazides had precedence in the steroid literature as reagents to make water-soluble derivatives that could be separated by simple aqueous extractions. These reagents are sold under the commercial name of Girard's reagents.[32] In particular, limiting amounts of Girard's reagent T (GRT) formed a hydrazone selectively with **5b** in AcOH over two hours at 40 °C. The hydrazone of **5b** was washed away from **5** with water, in a highly selective manner that eliminated the need for column chromatography (Scheme 7). The isolation yield for this step was 90% based on the initial amount of **5** in the mixture. The aqueous extract could be hydrolyzed under acidic condition to recover **5b** containing a small amount of **5**. Total recovery of the isomers from the reaction and hydrolysis was 96%. It was also discovered that when this separation procedure was performed at reflux in acetonitrile, with only a small amount of acetic acid for 4 h, one could obtain **5** in 98% yield following the same workup conditions; however, due to the price of acetonitrile at the time of production, it was not advantageous to use these conditions.

Table 4. Comparison of reagents required before (2006) and after (2011) the optimization of 5 and 5b to produce 1 kg of corannulene[22]

	2006		2011	
	reagent	kg	reagent	kg
reaction:	**4**	5.2	**4**	4.3
	oxalyl chloride	6.6	oxalyl chloride	4.2
	aluminum bromide	20	aluminum bromide	16
	dichloromethane	540	dichloromethane	150
workup:	water	910	water	92
	$MgSO_4$	40	Na_2SO_4	15
	sat. NaCl sol.	240	Celite	7.8
			Na_2CO_3	2.9
			toluene	67
yield:	N/A		73% (**5** + **5b** 2:1)	4.2
purification:	silica gel	780	AcOH	29
	hexane	1300	GRT	1.2
	dichloromethane	750	water	47
yield:	36% (**5**)	2.5	42% (**5**)	2.5
vol. yield:	reaction: 0.62%	total: 0.07%	reaction: 2.2%	total: 0.70%
E-factor:		1800		170

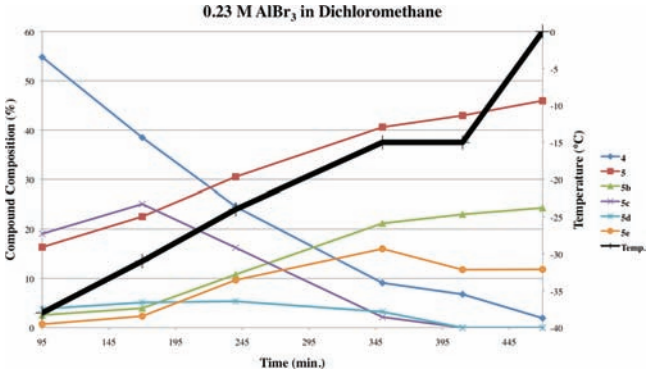
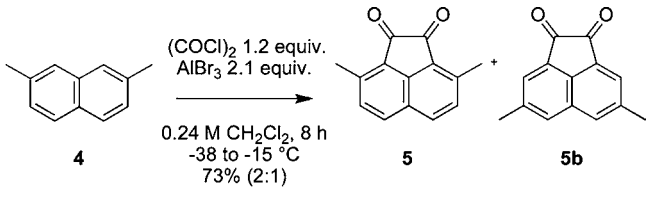


Figure 3. In process control of **4**, **5** and **5b**−**5e** composition (HPLC) along time/temp profile (Optimized).

Scheme 6. Preparation of isomers 5 and 5b



Synthesis of 1,6,7,10-Tetramethylfluoranthene (7). The next step of the synthesis was conversion of **5** to 1,6,7,10-tetramethylfluoranthene (**7**) through a crossed-aldol condensation followed by a Diels−Alder, retro Diels−Alder reaction cascade using norbornadiene (Scheme 8). Improvements to this step significantly improved volumetric productivity, which reduced the amount of solvents required. The amount of methanol required for the Knoevenagel condensation could be reduced by 50% compared to that previously reported[33] and still obtain the same yield (Table 5); however, decreasing the equivalents of 3-pentanone[34] and KOH from the reported value led to a decrease in yield. Another important factor in this step was the isolation of the hydroxy intermediate **6**. Careful neutralization of the reaction must be done to avoid protonation and elimination, leading to dimerization of the newly formed cyclopentadienone. Previous attempts to crack the dimer in the subsequent step were unsuccessful. Formation of the dimer dramatically decreases the yield.

Important to the optimization of the workup for the Diels−Alder/retro-Diels−Alder step was the realization that, with slow quenching of the final reaction mixture, one could precipitate and filter **7** at the end of the reaction. This eliminated the need for the extraction and column chromatography reported in the literature procedure. The final product was obtained in 99.8% purity after recrystallization from an *i*-PrOH/acetone mixture.

Radical Bromination of 6 To Yield 1,6,7,10-Tetrakis-(dibromomethyl)fluoranthene (7b). The literature bromination of **6** proceeded through a radical bromination using NBS and radical initiaton by benzoyl peroxide (BPO) in benzene (or carbon tetrachloride) with a 375 W tungsten lamp as the light source.[35] This step was challenging to produce on scale due to the safety issues associated with the solvents and with

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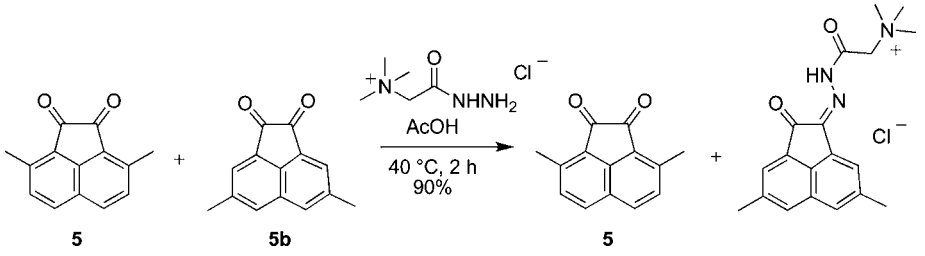
Scheme 7. Separation of 5 and 5b using Girard's Reagent in AcOH



Scheme 8. Optimization of 1,6,7,10-tetramethylfluoranthene (7)

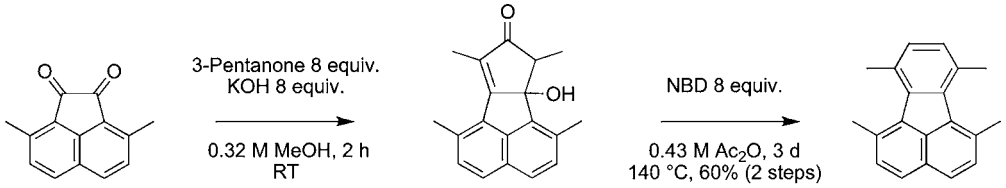


Table 5. Comparison of reagents required before (2006) and after (2011) for the optimization of 7 to produce 1 kg of corannulene[22]

	2006		2011	
	reagent	kg	reagent	kg
reaction:	**5**	2.5	**5**	2.5
	MeOH	88	MeOH	30
	KOH	16	KOH	16
	3-pentanone	8.3	3-pentanone	8.0
workup:	water	110	water	87
	sat. NaCl solution	34	HCl (32%)	30
	HCl (10%)	11		
	dichloromethane	120		
	$MgSO_4$	9.3		
reaction:	acetic anhydride	30	acetic anhydride	32
	NBD	8.4	NBD	8.6
workup:	water	74	water	7.4
	NaOH (10%)	52	NaOH (30%)	6.2
	DCM	50	MeOH	56
	sat. NaCl solution	54		
yield:	N/A		66% (7)[a]	2.1
purification:	silica gel	250	silica gel	2.1
	hexane	2000	cyclohexane	28
			isopropanol	17
			acetone	0.52
yield:	60% (7)	1.9	65% (7)[b]	2.0
vol. yield:	reaction: 1.4%	total: 0.05%	reaction: 3.0%	total: 0.64%
E-factor:		1500		160

[a]Assay: 94%; uncorrected yield: 70%. [b]Assay: 99.8%; purification yield: 99%.

Table 6. Comparison of reagents required before (2006) and after (2011) for the optimization of 8b to produce 1 kg of corannulene[22]

	2006		2011	
	reagent	kg	reagent	kg
reaction:	7	1.9	7	2.0
	NBS	14	NBS	16
	BPO	0.11	AIBN	0.06
	benzene	130	chlorobenzene	46
workup:	water	38	ethyl acetate	15
	dichloromethane	63		
	$MgSO_4$	19		
	sat. NaCl solution	46		
	$Na_2S_2O_3$	87		
purification:	silica gel	200	N/A	
	hexane	1400		
yield:	74% (**8b**)	4.8	73% (**8b**)	5.1
vol. yield.	reaction: 3.3%	total: 0.19%	reaction: 12%	total: 8.8%
E-factor:		410		12

performing a photochemical radical reaction.[36] Specifically, the radical initiator used, BPO, is less effective at stable radical production than other initiators and is not preferred on scale.[37] To overcome these safety issues a series of reactions were screened to try and avoid the need for radical initiators. The solvent of choice turned out to be chlorobenzene at 90−95 °C, but, unfortunately, the higher temperature did not obviate the use of light and a radical initiator, albeit clear that substantial thermal activation seemed to occur. The better stabilized radical initiator AIBN, available from the Vazo line of initiators at Dupont, showed good results at these higher temperatures on scale, and was selected (Table 6).

There were also hesitations that the light source would not be sufficient on such scale due to the heating mantle and depth of the 100-L reactor. Accordingly, many attempts to find brominating conditions without an extra light source were attempted but unsuccessful, even in the presence of AIBN. Fortunately, radical generation at the outer layer of the reactor sufficed to give a steady and robust process. On 100-L scale, three lamps were adequate to perform the bromination when shone directly into the solution.

An unforeseen problem arose when scaling the bromination from 10 to 50 g. The dark-red solution unexpectedly turned black and the optimized workup conditions failed to yield **8b** directly. Column chromatography of the mixture resulted in a 25−30% isolated yield of **8b** while the remainder of the crude

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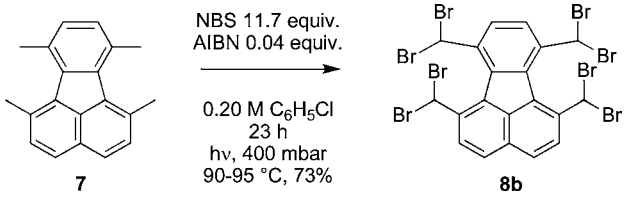
mixture stayed on the baseline. This was most likely due to the presence of HBr in the headspace that was responsible for the formation of side products in significant proportions. A slight vacuum of 400 mbar was applied and the reaction proceeded as expected (Scheme 9). The product was recrystallized using ethyl acetate, eliminating the column chromatography that was previously required. Given the sensitivity of the octabromo compound, a large-scale chromatography would not only have added cost and material waste from the silica, but likely would have led to some product decomposition.

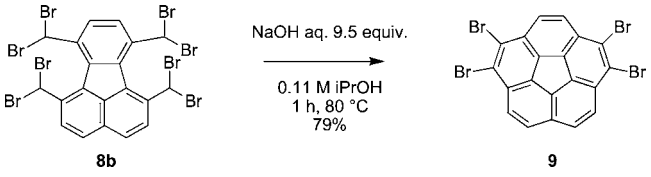
Scheme 9. Benzylic bromination of fluoranthene 7



Synthesis of 1,2,7,8-Tetrabromocorannulene (9). A strategic improvement for the ring closure of **8b** to form the first derivative containing the corannulene core, tetrabromocorannulene **9**, was reported by Sygula et al. using a dioxane/water mixture in the presence of base.[20] Nonetheless, there were still two main areas of optimization for this step: the low volume yield due to reaction concentrations of 20 mM and the cost and toxicity of dioxane as solvent.

In an attempt to overcome the issue of low concentration, the reaction was performed in a ratio of 1 g **8b** in 10 mL of a solvent mixture (H_2O:MeOH, H_2O:Toluene, H_2O:Dioxane, Toluene:MeOH) with varying bases (NaOH, NaOMe, KOH). These reactions resulted in polymerization of the starting material. The next consideration was portionwise addition of **8b** to the solvent mixture. Upon formation, the product **9** precipitates and allows the starting material to dissolve in the solvent. This would decrease the amount of solvent needed while having minimal effect on the yield. Unfortunately, the strategy proved wrong and instead polymerization of the starting material was the main product isolated upon filtration. A wider screening of solvents showed that isopropanol was a suitable replacement of the dioxane/water mixture, increasing the allowable reaction concentration from 20 mM to 112 mM (Scheme 10). Addition of **8b** to an isopropanol solution with sodium hydroxide at reflux led to the clean formation of **9** in a 79% yield (Table 7). The product was filtered and carried through to the next step without further purification.

Scheme 10. Ring closure of 8b to yield 1,2,7,8-tetrabromocorannulene 9



Reduction of Tetrabromocorannulene (9) to Corannulene (1). The final step of the synthesis, reduction of **9** to **1** had a number of hurdles to overcome.[38] One principal problem for the reaction was the excessive amounts of reagents, solvent, and reaction time required. Although zinc is relatively inexpensive compared to other metals, the large zinc dust excess (100 equiv) and amount of ethanol (8.8 mM) required to facilitate stirring proved to be a challenging environmental waste problem. Another difficulty with this reaction was the reported long reaction time of six days. Even after the use of excessive reagents and long reaction times, one would still isolate a mixture of side products that required column chromatography to purify.

Table 7. Comparison of reagents required before (2006) and after (2011) for the optimization of 9 to produce 1 kg of corannulene[22]

	2006		2011	
	reagent	kg	reagent	kg
reaction:	**8b**	4.8	**8b**	5.1
	NaOH	2.2	NaOH (30%)	6.8
	dioxane	190	isopropanol	40
	water	73		
workup:	water	380	water	19
	HCl (10%)	16	isopropanol	11
	dichloromethane	250		
	acetone	150		
yield:	83% (**9**)	2.5	79% (**9**)	2.5
vol. yield:	reaction: 0.95%	total: 0.24%	reaction: 4.9%	total: 3.0%
E-factor:		420		30

A recent paper by Thiemann[39] used zinc dust in the presence of ammonium formate and base to dehalogenated tetrabromobisphenol A (TBBPA), a hazardous pollutant, via transfer hydrogenation. These results led us to believe that a stoichiometric quantity of ammonium formate and zinc could have the same effect on corannulene, greatly reducing the amount of reagents and solvents required and shortening reaction time to just a few hours. Initial results appeared encouraging with **1** detected after only 2 h. Unfortunately the reaction did not proceed to completion and even after 2 days and up to 20 equiv of zinc powder, GC–MS and TLC identified that there was dibromocorannulene and monobromocorannulene still present in the reaction. Analysis of the reactor headspace indicated the presence of acid. It was hypothesized that HBr formation during the reaction was preventing further reduction of **9** and addition of zinc oxide might solve this problem and push the reaction to completion. We expected the ZnO and HBr to react and form zinc bromide and water. Unfortunately, the addition of ZnO did not have an effect on the reaction and an alternative reduction method was sought.

A paper by Spatola[40] showed that ammonium formate and Pd/C were successful at reducing haloaromatics through catalytic transfer hydrogenation. Successful reduction of **9** to **1** was achieved by replacing zinc with 5% palladium on carbon. A setback occurred upon scaleup from 1 to 10 g since formation of ammonium bromide was detected in the condenser. Due to our specific reactor configuration, salt accumulation would not be easy to remove safely during production, although these reaction conditions were otherwise efficient and scalable. To solve our specific infrastructure issue, we replaced ammonium formate with a triethylamine/formic acid mixture and further solvent screening showed pyridine was the best to solubilze the formed salts. A less costly alternative to pyridine is 3-picoline, which produced similar results and was used (Table 8) in the reduction of **9** (Scheme 11).[41]

CONCLUSION

The optimization and production of **1** has been demonstrated on scale. The key successes of the synthesis were to eliminate the

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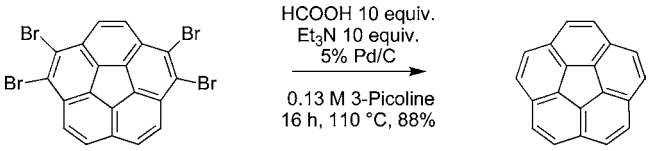
Table 8. Comparison of reagents required before (2006) and after (2011) for the optimization to produce 1 kg of corannulene[22]

	2006		2011	
	reagent	kg	reagent	kg
reaction:	**9**	2.5	**9**	2.5
	4% HCl	26	formic acid	1.7
	Zn	30	triethylamine	3.6
	KI	11	5% Pd/C	0.13
	EtOH	390	3-picoline	27
workup:	water	250	water	14
	dichloromethane	200	HCl (32%)	1.7
	$MgSO_4$	15		
purification:	silica gel	250	toluene	27
	hexane	1900	activated carbon	0.04
			Celite	0.16
yield:	90% (**1**)	1.0	88% (**1**)	1.0
vol. yield:	reaction: 0.19%	total: 0.03%	reaction: 3.5%	total: 1.3%
E-factor:		3100		75

Scheme 11. Reduction of 9 to corannulene using Pd/C



9 **1**

column chromatographies previously required for four of the eight steps as well as to find safer and less costly solvents and reagents. Careful evaluation of required solvent volume in the synthesis of **1** starting from [alpha]-chloro-m-xylene **2** improved the average concentration of each step from 0.04 to 0.24 M. A total of 1.3 kg of **1** were isolated in an 8.7% yield over nine steps with the average yield per step being 75% (Scheme 12).[42]

In retrospect, the present process has come a long way since the discovery synthesis of Lawton and Barth. It offers a scalable batch process amenable to a simple pilot-scale facility and has led to the production of corannulene on kilogram scale. Nonetheless, there is still much room for improvement and optimization, which bodes well for the future. In particular, a more selective diacylation of **4** to **5** could reap great benefits in cost and scalability. In addition at present the conversion of **7** to **1** goes through a multistep process, but a dehydrogenative benzylic coupling and aromatization in one transformation, perhaps by a flow process may be feasible. Such a direct oxidative benzylic coupling by CH activation of the unfunctionalized methyl groups would consititute a new carbon−carbon bond-forming reaction with great synthetic utility. If these two hurdles were to be addressed by proper catalysts or reaction conditions, another improvement by 2 orders of magnitude in material costs could be gained. This conversion of the production of corannulene from milligram scale in 1966 to kilogram scale in 2011 also marks the transition of corannulene from an esoteric molecular object of academic interest into a chemical entity with a potential engineering/commercial future.

EXPERIMENTAL SECTION

General. Starting materials were obtained from commercial suppliers and were used without further purification. HPLC analyses were performed on an Agilent Series 1100 liquid chromatograph equipped with a UV detector. NMR data obtained were identical to those reported in the literature. Yield calculation based on HPLC purity, or assay if indicated. Mole amount reported has been corrected based on purity.

3-Hydroxy-3-methyl-4-(3-methylphenyl)butanal Dimethyl Acetal (3). Under a N_2 atmosphere, a 100-L reaction vessel, magnesium turnings (2.15 kg, 88.2 mol) and anhydrous diethyl ether (11.3 kg; test for peroxides was negative) were added at a temperature of 15−25 °C. To this suspension α-chloro-*m*-xylene (311 g, 2.12 mol) was added at once. The reaction started immediately as observed by temperature rise to reflux and turbidity. When the reaction started, a solution of α-chloro-*m*-xylene (9.72 kg, 66.4 mol) in diethylether (21.9 kg) was added at an internal temperature (IT) of 33−36 °C over 2 h. The suspension was stirred for 30−60 min (IT = 33−36 °C); then a solution of acetylacetaldehyde-dimethylacetal (95%, 8.25 kg, 59.3 mol) in diethylether (18.7 kg) was added (IT = 33−36 °C) over 2 h. The suspension was cooled to an internal temperature of 15−25 °C and stirred at this temperature for 50−70 min. The suspension was then added to a precooled (0−5 °C) solution of ammonium chloride (35.6 kg, 666 mol) in water (100 kg) while stirring vigorously (IT = 0−5 °C; *caution: H_2 gas evolution!*). The mixture was stirred until gas evolution ceased and two clear layers were obtained. The aqueous phase was extracted two times with MTBE, and the organic layers were combined and dried over sodium sulfate. The sodium sulfate was filtered, and the organic layer was evaporated to dryness at a bath temperature of 30−40 °C to yield 13.5 kg (HPLC purity 89% 3-hydroxy-3-methyl-4-(3-methylphenyl)butanal dimethyl acetal (**3**) [12.0 kg, 85% HPLC corrected yield]).

2,7-Dimethylnaphthalene (4). In a 100-L reaction vessel, **3** (15.1 kg, purity 86% [13.0 kg, 54.8 mol]) was dissolved in acetic acid (74.2 kg) at 20−25 °C. Sulfuric acid (97%, 9.10 kg) was added to the solution of **3** slowly over 10 min. The reaction mixture was refluxed (IT = 118 °C) for 30 min then cooled to an internal temperature of 38−43 °C and the acetic acid (64.3 kg) was distilled (IT = 107 °C) under reduced pressure (50−70 mbar). The remaining mixture was poured into ice water (130 kg) and extracted twice with toluene (110 kg total). The organic phases were combined and washed with a sodium bicarbonate solution (3.7 kg) then sodium chloride solution (700 g). The organic phase was then dried using magnesium sulfate (5.0 kg) and filtered, and then the toluene was completely removed under reduced pressure. The resulting solid (10.1 kg) was recrystallized using ethanol (31 kg) to yield 6.37 kg of a light-brown solid (HPLC purity 99% 2,7-dimethylnaphthalene (**4**) [6.32 kg, 74% HPLC corrected yield]). Mp 95−96 °C, ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.49 (s, 6 H), 7.22 (d, 2 H, J = 8.0), 7.50 (s, 2 H), 7.65 (d, 2 H, J = 8.0); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.7, 126.3, 127.2, 127.4, 130.0, 134.0, 135.4.[43]

3,8-Dimethylacenaphthenequinone (5) and 4,7-Dimethylacenaphthenequinone (5b). Dichloromethane (66.5 kg) was charged to a 100-L reaction vessel and then cooled to an internal temperature of −40 to −30 °C. Aluminum bromide (10.3 kg, 38.2 mol) was added and stirred at this temperature for at least 30 min. Meanwhile, a solution of 2,7-dimethylnaphthalene (2.78 kg, purity 100% [2.78 kg, 17.8 mol])

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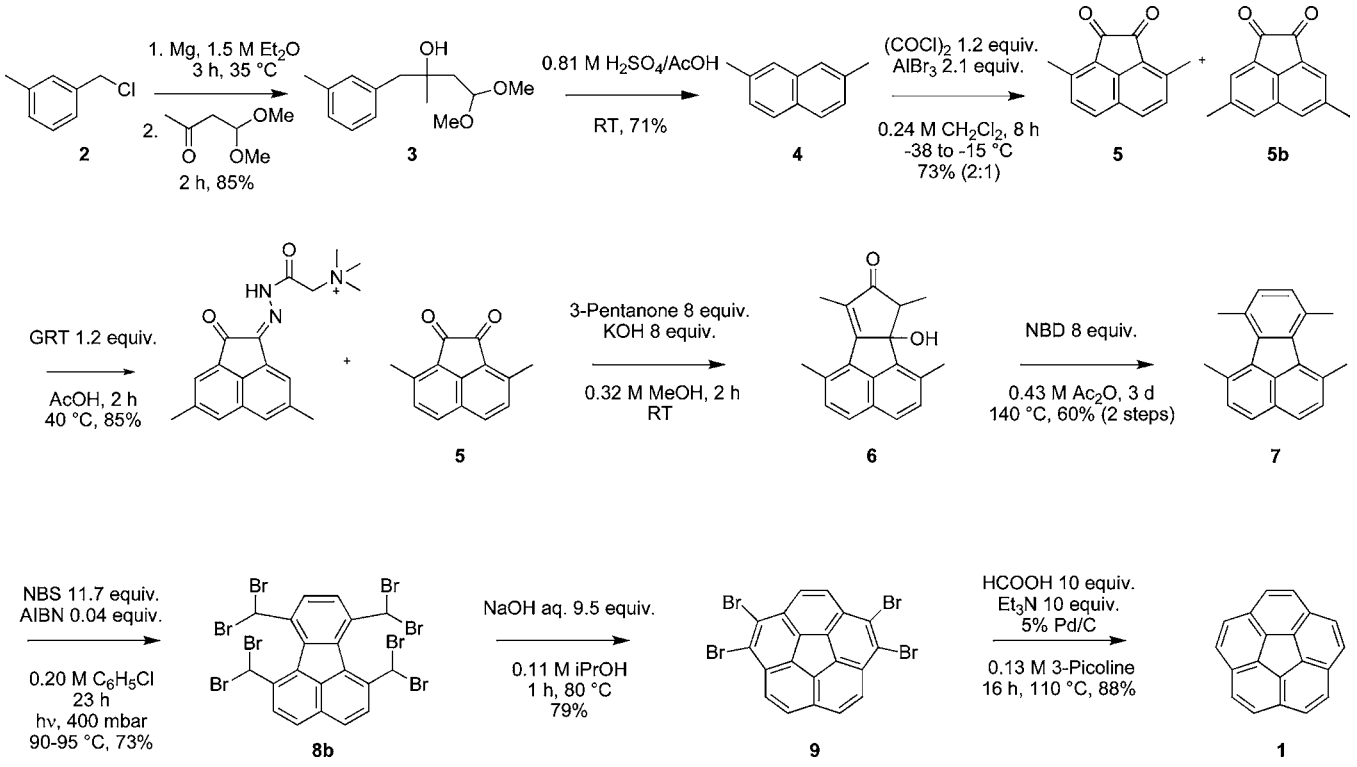
Scheme 12. Optimized synthesis of corannulene (1)



in dichloromethane (33.2 kg) was prepared. Oxalyl chloride (2.73 kg, 21.0 mol) was added to this solution, and the solution was added dropwise to the aluminum bromide solution, maintaining an internal temperature below −35 °C. When approximately 90% of the oxalyl chloride solution was added, a temperature gradient was started. The jacket temperature was programmed to increase from −45 °C to −15 °C within 4 h. Afterwards, the internal temperature was kept at −15 to −20 °C and HPLC in-process controls were taken every hour until there was less than 7% starting material compared to product, approximately 7−8 h. Water (12.0 kg) was slowly added then the reaction was allowed to warm to room temperature. The reaction mixture was filtered through Celite (5.0 kg) then the Celite filter cake was washed with water (30 kg) and dichloromethane (30 kg). The layers were separated and the aqueous layer was extracted once more with dichloromethane (13 kg). The two organic layers were washed consecutively with water (20 kg) and the combined layers were dried with sodium sulphate (5.0 kg). The suspension was filtered and the filter cake was washed with dichloromethane (6.4 kg). A "100-L reaction vessel was charged with the filtrate and heated to an internal temperature of 36−42 °C and the solvent was distilled. After distilling 118 kg, toluene (32 kg) was added. The jacket temperature was increased from 55 to 90 °C within 2 h. When the internal temperature reached 85−90 °C, the jacket temperature was cooled to 80 °C then a solution of sodium carbonate (2.8 kg, 26.2 mol) in water (37 kg) was added. The mixture was heated until the internal temperature reached 75−80 °C, then the layers were separated and the organic layer was washed with water (10 kg). The aqueous layer was separated and the organic layer was distilled at an internal temperature of 81−86 °C until the product began to crystallize. The suspension was then cooled to an internal temperature of 0−5 °C within 4 h and stirred overnight at that temperature. The suspension was filtered and the white filter cake was washed via reactor with toluene (10 kg). The wet product was dried for 14 h at 50 °C and <10 mbar to yield 2.33 kg yellow needles (HPLC purity 71.1% 3,8-dimethylacenaphthenequinone (**5**) 28.9% 4,7-dimethylacenaphthenequinone (**5b**) [2.33 kg, HPLC corrected yield of the isomer mixture: 62%]). The mother liquour was concentrated to 3 L, cooled to 0 °C, and kept at this temperature overnight. The suspension was filtered and washed with toluene (1 kg) then dried at 50 °C and <10 mbar to yield 180 g yellow-brown powder (HPLC purity 64.7% 3,8-dimethylacenaphthenequinone (**5**) 33.8% 4,7-dimethylacenaphthenequinone (**5b**) [0.177 kg, HPLC corrected yield of the isomer mixture: 4.7%]).

Separation of 3,8-Dimethylacenaphthenequinone (5) and 4,7-Dimethylacenaphthenequinone (5b). Acetic acid (31.5 kg) and a mixture of isomers **5** and **5b** (6.00 kg, purity 69% (**5**) [4.1 kg (**5**), 19.7 mol (**5**)]) was charged to a 100-L reaction vessel and heated to 40 °C for at least 30 min. During this time, a solution of Girard's Reagent T (1.73 kg, 10.3 mol, 1.2 equiv of **5b**) in 9.55 kg acetic acid was prepared. This solution was added dropwise to the isomer mixture solution over 2 h. The reaction continued to stir for an additional 2 h, then water (60.0 kg) was slowly added to quench the solution over a period of 30 min. The suspension was filtered, washed with 8 kg water, and then dried at <2 mbar overnight to result in 3.72 kg **5** (HPLC assay 97% 3,8-dimethylacenaphthenequinone (**5**) [3.67 kg, 90% HPLC corrected yield]). Mp 204−205 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.87 (s, 6H), 7.49 (d, 2H, J = 8.28 Hz), 8.03 (d, 2H, J = 8.28 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.12, 76.58, 77.00, 77.42, 124.29, 127.47, 130.63, 131.73, 137.57, 147.10, 188.80.

To the mother liquor, hydrochloric acid (55.7 kg) in water (24.0 kg) was added and stirred at room temperature for 3 h. The precipitate was filtered then dried at <2 mbar overnight to

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yield a mixture of isomers **5**:**5b** (1.88 kg) of 1:4. Total recovery for this step for **5** was 99% (**5** + **5b** 93%).

1,6,7,10-Tetramethylfluoranthene (6). Methanol (20 kg) was charged to a 100-L reaction vessel, then KOH (11.0 kg, 177 mol) was added in portions. The solution was heated to 60−80 °C until the KOH dissolved. The solution was then cooled to 20 °C, and 3-pentanone (5.45 kg, 61.9 mol) was added. 3,8-Dimethylacenaphthenequinone (1.70 kg, assay 98% [1.67 kg, 7.86 mol]) was slowly added, and a brown solution was obtained. The mixture was stirred at 18−25 °C for at least 2 h. The reaction mixture was cooled to 0 °C, and a previously cooled (−3 °C) solution of water (44 kg) and HCl (32%, 20 kg) was added dropwise (so that the internal temperature was less than 20 °C) until the color of the solution changed to a yellow-green and pH was between 5 and 7. The suspension was stirred for 30−60 min at 18−22 °C and then filtered, and the filter cake was washed with water (15 kg). The product was dried at 40 °C and <10 mbar for 24 h. The vessel was charged with the dried intermediate (2.17 kg), acetic anhydride (21.0 kg), and 2,5-norbornadiene (5.8 kg). The reaction mixture was heated to reflux (135−140 °C) for 2−3 days and then cooled to 20−25 °C. A solution of 30% NaOH (4.2 kg) and water (2.5 kg) was added slowly dropwise. The reaction mixture was allowed to stir overnight at 15−30 °C and then distilled at 200 mbar and at an internal temperature of 70 °C (distillate 16 kg). Water (2.5 kg) was added, and the internal temperature was raised to 88 °C; then vacuum (300 mbar) was slowly applied. The mixture was cooled to an internal temperature of 20−25 °C, and distillate (6.7 kg) was collected. Methanol (2.5 kg) was added to precipitate **6**, and the dark-brown suspension was filtered and washed with additional MeOH (2.5 kg). The reactor was charged with the filter cake and methanol (25.5 kg) and then was heated to reflux for 1 h. The suspension was cooled to 20−25 °C and stirred at this temperature overnight and then filtered, and the filter cake was washed with additional MeOH (2.1 kg). The product was dried at 40 °C and <10 mbar for 4 h to yield 1.35 kg (HPLC assay 94.5% 1,6,7,10-tetramethylfluoranthene (**7**) [1.28 kg, 63% HPLC corrected yield]).

For further purification a 50-L reaction vessel was charged with **7** (1.99 kg, assay 94% [1.87 kg, 7.22 mol]) and cyclohexane (26.5 kg). A dark-brown suspension was obtained and then filtered through a silica gel plug (2.0 kg) with 800 mbar. The filtrate was evaporated, and the distilled cyclohexane was used to wash the silica gel until no **6** can be detected on TLC. The residue was then heated in isopropanol (13.9 kg) at 79 °C. Acetone (0.50 kg) was added dropwise until a solution was obtained; then the solution was cooled to 20−25 °C and stirred at this temperature overnight. The suspension was filtered, and the filtrate was washed with cooled isopropanol (2.3 kg). The product was dried at 50 °C and <10 mbar overnight to yield 1.84 kg (HPLC assay 99.8% 1,6,7,10-tetramethylfluoranthene (**7**) [1.84 kg, 99% HPLC corrected yield]). Mp 140.5−143.5 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.74 (s, 6H), 2.84 (s, 6H), 7.13 (s, 2H), 7.35 (d, 2H, J = 8.28), 7.67 (d, 2H, J = 8.28); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.30, 25.13, 126.15, 126.60, 129.63, 130.67, 131.83, 132.00, 133.67, 134.88, 139.91

1,6,7,10-Tetrakis(dibromomethyl)fluoranthene (7). A 100-L reaction vessel was charged with chlorobenzene (55.5 kg) and 1,6,7,10-tetramethylfluoranthene (2.47 kg, assay 99.8% [2.47 kg, 9.56 mol]). The solution was heated to 70−75 °C while illuminating with three 350 W spot bulbs in a distance of 30 cm for the duration of the reaction sequence. AIBN (25.0 g, 0.152 mol) and NBS (20.0 kg, 112 mol) were added, and a vacuum (400 mbar) was applied. The mixture was heated to an internal temperature of 90 °C and after 15−30 min an exothermic reaction was detected. The jacket temperature was set to <98 °C until the internal temperature decreased since decomposition of the product occurs at temperatures above 100 °C. The mixture was stirred vigorously at 90−95 °C, and the reaction was monitored by thin layer chromatography. Additional AIBN (25.0 g, 0.152 mol) was added after 3 and 10 h. After 23 h the suspension was cooled to 40−45 °C, and the suspension was filtered. The filtrate was evaporated at 70 °C (120 mbar to 8 mbar), and the distillate (20 kg) was used to wash the filter cake. Ethyl acetate (8 kg) was added, and then the solvent was evaporated at 70 °C (120 mbar to 8 mbar). Additional ethyl acetate (2 kg) was added, and then the suspension was stirred for 1 h at 70 °C before cooling to 18−25 °C. The suspension was left to stir at this temperature overnight, then filtered and washed with ethyl acetate (3.8 kg). The wet product was dried at 40 °C and <10 mbar for 12 h to yield 6.40 kg (HPLC purity 92% 1,6,7,10-tetrakis(dibromomethyl)fluoranthene (**8**) [5.93 kg, 70% HPLC corrected yield]). Mp > 300 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 2H), 7.22 (s, 2H), 7.99 (d, ^3J = 8.5 Hz, 2H), 8.22 (s, 2H), 8.28 (d, ^3J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 38.5, 39.0, 127.6, 130.1, 130.2, 131.5, 131.8, 132.3, 136.5, 137.9.

1,2,7,8-Tetrabromocorannulene (8). A 50-L reaction vessel was charged with isopropanol (24.9 kg) and 1,6,7,10-tetrakis(dibromomethyl)fluoranthene (3.19 kg, purity 93% [2.97 kg, 3.35 mol]). The suspension was heated to an internal temperature of 77−82 °C. A NaOH solution (30% aq, 4.25 kg, 31.9 mol) was added dropwise over 40 min; the reaction mixture was allowed to stir at 77−82 °C for 55−65 min. The suspension was slowly cooled to 20−25 °C over 90−120 min and then filtered through a glass filter, and the filter cake was washed with water (12.0 kg) then isopropanol (6.9 kg). The product was dried at 50 °C and <10 mbar for 24 h to yield 1.90 kg (HPLC purity 79% 1,2,7,8-tetrabromocorannulene (**9**) [1.49 kg, 79% HPLC corrected yield]). Mp 338−340 °C dec, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 2H), 7.95 (d, ^3J = 8.9 Hz), 7.85 (d, ^3J = 8.9 Hz, 2H). ^{13}C NMR was not obtained due to poor solubility.

Corannulene (9). A 50-L reaction vessel was charged with 1,2,7,8-tetrabromocorannulene (4.0 kg, purity 77%, [3.32 kg, 5.87 mol[44]]), 3-picoline (42.0 kg), formic acid (2.62 kg, 55.8 mol), triethylamine (5.76 kg, 56.6 mol), and 5% Pd/C (50% water, 200 g, 0.41 mol). The suspension was heated to reflux and stirred for 16 h, until the reaction was complete. The mixture was cooled to an internal temperature of 20−25 °C, and the solid was filtered through a glass filter and then washed with 5.7 kg 3-picoline. The filtrate was returned to the reactor and heated to an internal temperature of 73 °C while applying a vacuum of (p_{start} = 100 mbar) to remove 45 kg of 3-picoline so that crystallization occurred. Upon crystallization of the product, toluene (23 kg) and a mixture of HCl (32%, 2.7 kg) in water (14 kg) was added until the pH of the water phase was 3. The mixture was heated to an internal temperature of 83−87 °C, and activated carbon (57 g) was added. This suspension was stirred for 10 min, and then Celite (250 g) was added and stirred for an additional 10 min. The mixture was filtered through a Celite plug under pressure (700 mbar), and the filtrand was washed with toluene (10 kg). The filtrate was transferred back into the reactor and heated to an internal temperature of 83−87 °C. The organic phase was washed twice with water (5.7 kg total) and then filtered (IT = 86−90 °C)

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through a glass funnel to remove the precipitate. The filtrate was transferred back to the reactor, and the organic phase was washed one last time with 15 kg water (IT = 86−90 °C); then the organic layer was distilled (24 kg) at an internal temperature of 87−93 °C under reduced pressure (p_{start} = 800 mbar, p_{end} = 530 mbar) until the product started to crystallize. The mixture was heated to reflux, and additional toluene (3.5 kg) was added. A clear orange-brown solution was obtained. The solution was cooled using a ramp (jacket temperature = 100 °C to jacket temperature = 70 °C) during 3 h and then cooled to jacket temperature = 15 °C and stirred for 15 h. The precipitate was filtered, and the filtrand was washed with toluene (0.16 kg) and then dried at 40 °C under vacuum for 21 h to yield 1.33 kg pale-yellow solid (HPLC purity 98% corannulene (**1**) [1.30 kg, 88% HPLC corrected yield]). Mp 268−269 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 127.2, 130.8, 135.8.

■ ASSOCIATED CONTENT

Supporting Information

HPLC methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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facility ammonium formate and a cheaper solvent could be implemented with great benefit to the overall process.
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