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# Progress toward the Total Synthesis of Ingenol: Construction of the Complete Carbocyclic Skeleton

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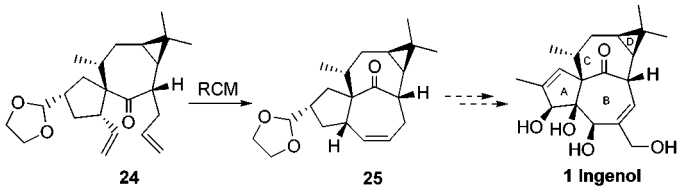
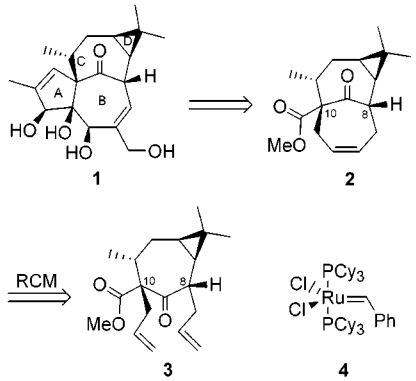
## ABSTRACT




**The complete carbocyclic skeleton of ingenol is assembled via a route that employs ring-closing metathesis (RCM) to close the strained "inside-outside" BC ring system (i.e., 24 → 25).**

Ingenol (**1**, Scheme 1), isolated and characterized by the Hecker group in 1968,[1] has attracted considerable interest from both the chemical and biological communities. Like the phorbol esters, various ingenol esters have been shown to mimic diacylglycerol and function as PKC activators.[2] Furthermore, many possess potent tumor promoting,[3] anti-leukemic,[4] and anti-HIV[5] properties. Hence, efficient synthetic access to these natural products and various synthetic analogues will promote the development of new therapeutic agents. However, despite the efforts of many groups, a complete total synthesis of **1** has yet to be reported.

**Scheme 1**




While the high degree of oxygenation, notably the *cis*-triol, represents a formidable synthetic challenge, the most imposing obstacle is construction of the highly strained "inside-outside" BC ring system. Successful approaches to the BC ring junction have generally relied upon fragmentation and rearrangement strategies,[6,7] while attempts at direct alkylations to construct the *trans* bridgehead all resulted in *cis* stereochemistry.[8] To date, synthesis of the complete ingenol tetracyclic carbon skeleton has only been achieved by Funk and co-workers.[7] In addition, very elegant work from the Winkler group has led to several ingenol analogues

(1) Hecker, E. *Cancer Res.* **1968**, *28*, 2338.
(2) Hasler, C. M.; Acs, G.; Blumberg, P. *Cancer Res.* **1992**, *52*, 202.
(3) Hecker, E. *Pure Appl. Chem.* **1977**, *49*, 1423−1431.
(4) Kupchan, S. M.; Uchida, I.; Branfman, A. R.; Dailey, R. G.; Fei, B. Y. *Science* **1976**, *191*, 571.
(5) Fujiwara, M.; Ijichi, K.; Tokuhisa, K.; Katsuura, K.; Shigeta, S.; Konno, K. *Antimicrob. Agents Chemother.* **1996**, *40*(1), 271−273.
(6) (a) Winkler, J. D.; Henegar, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 2850. (b) Rigby, J. H.; Claire, V. S.; Cuisiat, S. V.; Heeg, M. J. *J. Org. Chem.* **1996**, *61*, 7992. (c) Tanino, K.; Kuwajima, I.; Nakamura, T.; Matsui, T. *J. Org. Chem.* **1997**, *62*, 3032.
(7) (a) Funk, R. L.; Olmstead, T. A.; Parvez, M. *J. Am. Chem. Soc.* **1988**, *110*, 3298. (b) Funk, R.; Olmstead, T. A.; Parvez, M.; Stallman, J. B. *J. Org. Chem.* **1993**, *58*, 5873.

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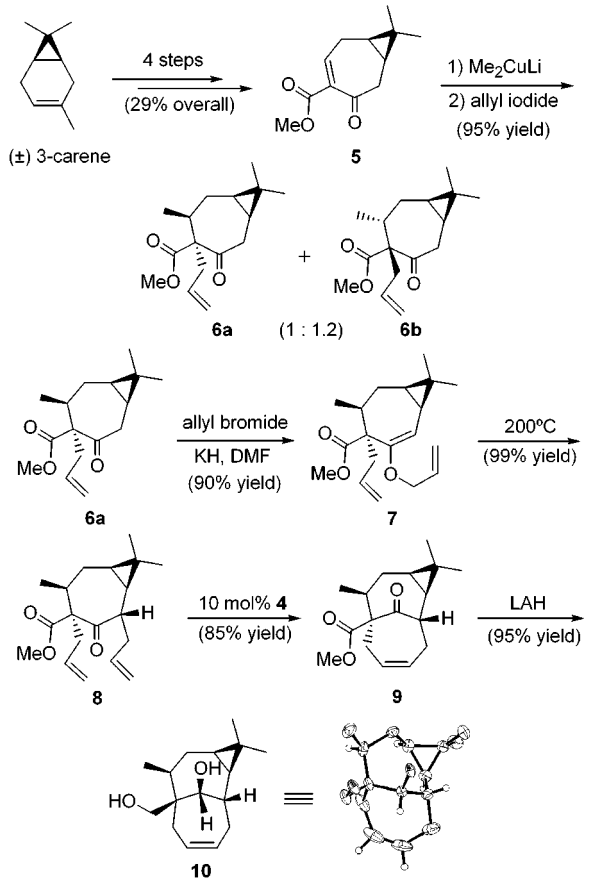
containing both the inside-outside BC ring junction and the *cis*-triol functionality.[9]

In contemplating a synthesis of the BC ring system, we became intrigued by the notion of establishing the *trans* relationship between C(8) and C(10) on a cyclic precursor (e.g., **3**, Scheme 1) and subsequently closing the B ring via a robust cyclization protocol like ring-closing metathesis (RCM).[10−12] Specifically, we were curious if application of the RCM protocol to diene **3** would furnish the strained inside-outside bicycle **2**.[13] While this work was in progress, a similar metathesis strategy to the ABC ring system was reported by Kigoshi.[14]

To explore this hypothesis, 3-carene was advanced to cycloheptenone **5** following the procedure of Funk (Scheme 2).[7a] Treatment of **5** with lithium dimethyl cuprate followed

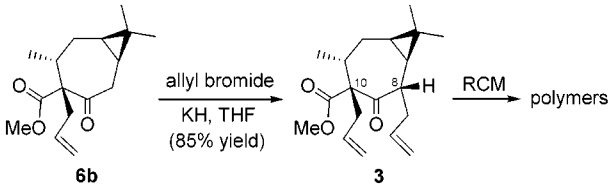
**Scheme 2**




by trapping of the resulting enolate with allyl iodide gave rise to $\beta$-keto esters **6a** and **6b** as a 1:1.2 mixture of diastereomers. Uncertain of the relative stereochemistry present in **6a** and **6b**, both esters were similarly advanced with the hope of obtaining this information from later intermediates. Ester **6a** was alkylated with allyl bromide to provide enol ether **7**, which upon heating smoothly underwent Claisen rearrangement to furnish **8** as a single diastereomer. Heating a dichloromethane solution of **8** and 10 mol % Grubbs's catalyst (**4**) to reflux provided ring-closed product **9** in good yield. Reduction of **9** furnished diol **10**, the structure of which was established by single-crystal X-ray analysis. Inspection of the crystal structure revealed that **10** contained the undesired "outside-outside" stereochemistry; thus, rigorously establishing the relative stereochemistry of **6a** and **8**.

Next, we focused our efforts on advancing the remaining diastereomer **6b**. Since studies of three-component reactions on cyclic enones have shown that the electrophile is typically trapped *trans* to the nucleophile,[15] we were confident that compound **6b** possessed the correct stereochemistry to furnish the desired RCM precursor **3**. Unlike **6a**, alkylation of **6b** gave rise exclusively to C-alkylated product **3** (Scheme 3). Unfortunately, all attempts to construct the BC ring system using RCM on substrate **3** were unsuccessful.

**Scheme 3**




Having established that diene **3** was not a suitable precursor to the BC ring system, computational studies were performed to identify a more viable cyclization substrate. Conformational searches[16] of potential candidates using the Merck Molecular Force Field (MMFF)[17] suggested that inclusion of the A ring would facilitate construction of the inside-outside BC ring system.[18] To explore this prediction, we initiated an approach to **12** wherein a Diels−Alder reaction between *exo*-olefin **14** and cyclopentadiene (**15**) was envisioned to simultaneously introduce the A ring and the functionality needed for the RCM chemistry (Scheme 4).

(8) (a) Paquette, L. A.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 6192. ( b) Mehta, G.; Pathak, V. P. *J. Chem. Soc., Chem. Commun.* **1987**, 876. (c) Harmata, M.; Elahmad, S.; Barnes, C. L. *Tetrahedron lett.* **1995**, *36*, 1397. (d) Rigby, J. H.; Cuisiat, S. V. *J. Org. Chem.* **1993**, *58*, 6286. (e) Rigby, J. H.; Rege, S. D.; Sandanayaka, V. P.; Kirova, M. *J. Org. Chem.* **1996**, *61*, 842.

(9) Winkler, J. D.; Sanghee, K.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296.

(10) (a) Grubbs, R. H.; Fu, G. C. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (b) Grubbs, R. H.; Schwab, P.; France, M. B.; Ziller, J. W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*(18), 2039.

(11) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; Dimare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (b) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899.

(12) For a recent review, see: Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371.

(13) For an application of RCM to a different inside-outside system, see: Krafft, M. E.; Cheung, Y.-Y.; Juliano-Capucao, C. A. *Synthesis* **2000**, 1020.

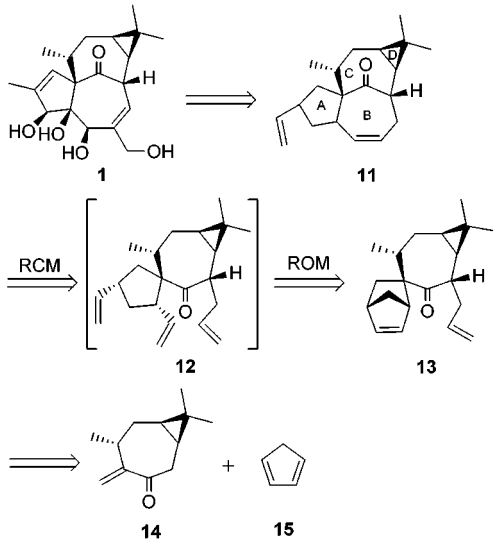
(14) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett.* **2000**, *41*, 3927.

(15) Boeckman, R. K. *J. Org. Chem.* **1973**, *38*, 4450.

(16) Calculations were performed using Spartan Version 5.1, Wavefunction Inc. 18401 Von Karman Ave. Suite 370, Irvine, CA 92612.

(17) Halgren, T. A. *J. Comput. Chem.* **1996**, *17*, 490.

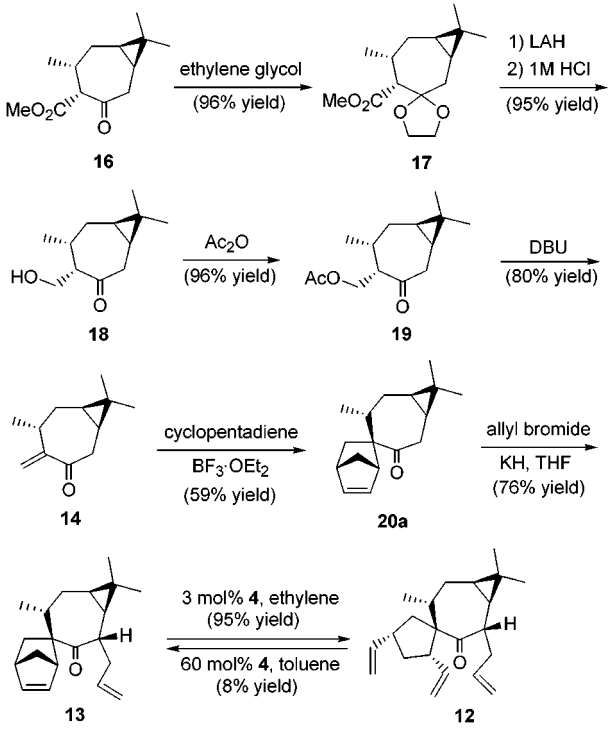
**Scheme 4**




Thus, tandem ring-opening ring-closing metathesis (ROM-RCM) of **13** would furnish the tetracyclic ingenol skeleton **11**.[19]

Studies commenced with known $\beta$-keto ester **16** (Scheme 5),[7a,20] which was converted to the corresponding ketal **17**.[21,22]

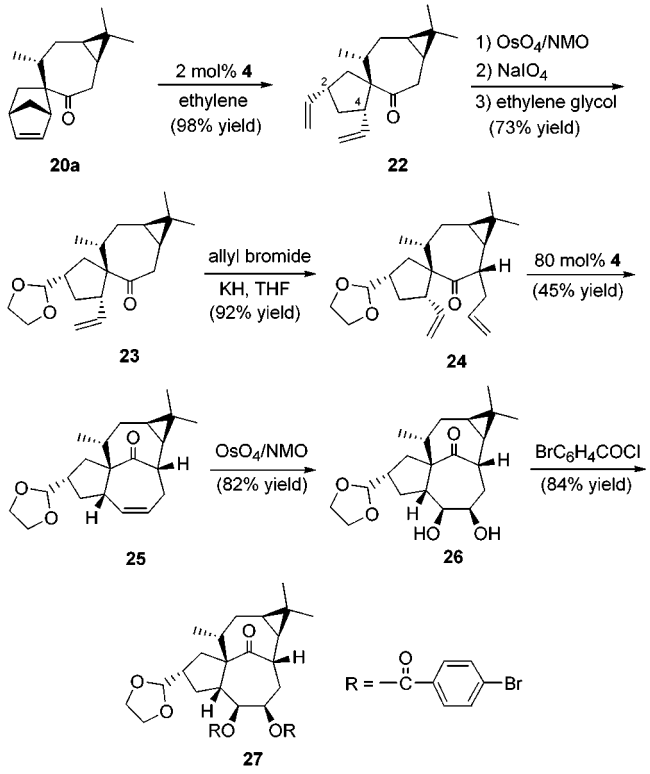
**Scheme 5**




Reduction of **17** followed by hydrolysis of the ketal delivered alcohol **18** in near quantitative yield. Acetylation of the alcohol followed by subsequent elimination furnished *exo*-olefin **14**. After considerable experimentation, it was found that boron trifluoride diethyl etherate effectively catalyzed the Diels−Alder reaction between **14** and cyclopentadiene (**15**) to provide a ternary mixture of diastereomers (**20a**,**b**,**c**) in a ratio of 20:8:1, respectively. We were delighted to find that the major constituent **20a** possessed the desired stereochemistry.[23] Alkylation of **20a** with allyl bromide furnished **13**, the precursor for the tandem ROM-RCM. Upon exposure of **13** to various ROM-RCM conditions under an atmosphere of ethylene, only ring-opening metathesis was observed, thereby providing triene **12** in excellent yield. Further exposure of this triene to various RCM conditions did not result in the desired product but rather regenerated norbornene **13** as the only isolable product in 8% yield.

In an effort to prevent reversion to **13**, efforts focused on masking the C(2) olefin prior to attempted RCM. To this end, ring-opening metathesis of **20a** under an atmosphere of ethylene gave rise to diene **22** in excellent yield (Scheme 6). Regioselective dihydroxylation of the C(2) olefin followed

**Scheme 6**




by oxidative cleavage provided the corresponding aldehyde, which was protected to afford acetal **23**. Alkylation of **23** proceeded smoothly to afford RCM precursor **24**. Gratifyingly, following careful optimization, exposure of **24** to **4** (four additions of 20 mol % **4** every 45 min) in refluxing toluene led to the elusive inside-outside ring system **25**. Dihydroxylation of **25** followed by esterification with *p*-bromobenzoyl chloride delivered dibenzoate **27**, the structure of which was confirmed by single-crystal X-ray analysis (Figure 1).

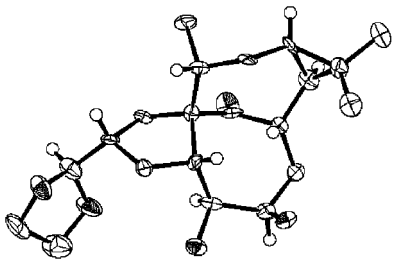


**Figure 1.** Crystal structure of **27** (benzoates removed for clarity).

In conclusion, the carbocyclic skeleton of ingenol has been successfully constructed using ring-closing metathesis. In addition, the A and B rings in **25** have the appropriate functionality to allow for elaboration to the natural product. Current efforts are directed toward developing a more efficient approach to **24** and advancing **25** to **1**; progress along these lines will be reported in due course.

**Acknowledgment.** We are pleased to acknowledge the support of this investigation by Bristol-Myers Squibb, Yamanouchi, Pfizer, Merck and the Camille and Henry Dreyfus Foundation for a Teacher-Scholar Award. J.L.W. is a fellow of the Alfred P. Sloan Foundation.

**Supporting Information Available:** Experimental procedures and spectral data pertaining to all new compounds and crystallographic data for **10**, **17**, **21**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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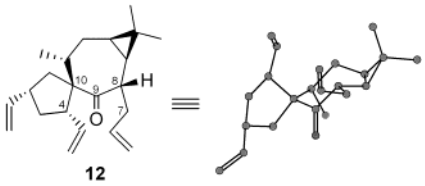
(18) A conformational search of precursor **3** illustrated that the two internal olefinic carbons are oriented 4.2 Å away from each other. With the installation of the A ring, the C ring conformation was dramatically twisted at quaternary center C(8), imparting a dihedral angle between C(8)−C(7) and C(10)−C(4) of 79.9°. Furthermore, the distance between the two internal olefinic carbons was reduced to 3.8 Å.



**12**

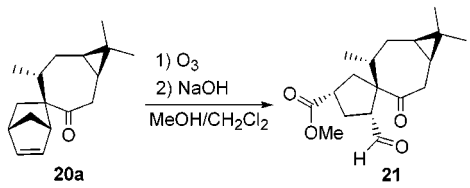
(19) (a) Blechert, S.; Stragies, R. *Synlett* **1998**, 169. (b) Schrock, R. R.; Hoveyda, A. H.; Weatherhead, G. S.; Ford, J. G.; Alexanian, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1828.

(20) $\beta$-keto ester **16** is actually isolated from a mixture of four diastereomers produced using the literature procedure (See ref 7a). However, it was subsequently discovered that the corresponding ketals were more readily separated. Thus, the diastereomeric mixture was carried forward on a preparative scale.

(21) The ketals were separated by silica gel chromatography. Four diastereomeric ketals were eluted in the ratio of 43:23:18:16. Only the major diastereomer **17** was advanced.

(22) The stereochemistry of **17** was unambiguously determined by X-ray crystallography.

(23) Ozonolysis of the major diastereomer **20a** gave rise to a crystalline compound **21**, the structure of which was established by X-ray crystallography. For spectral data pertaining to **20b** and **20c**, see Supporting Information.




**20a** **21**