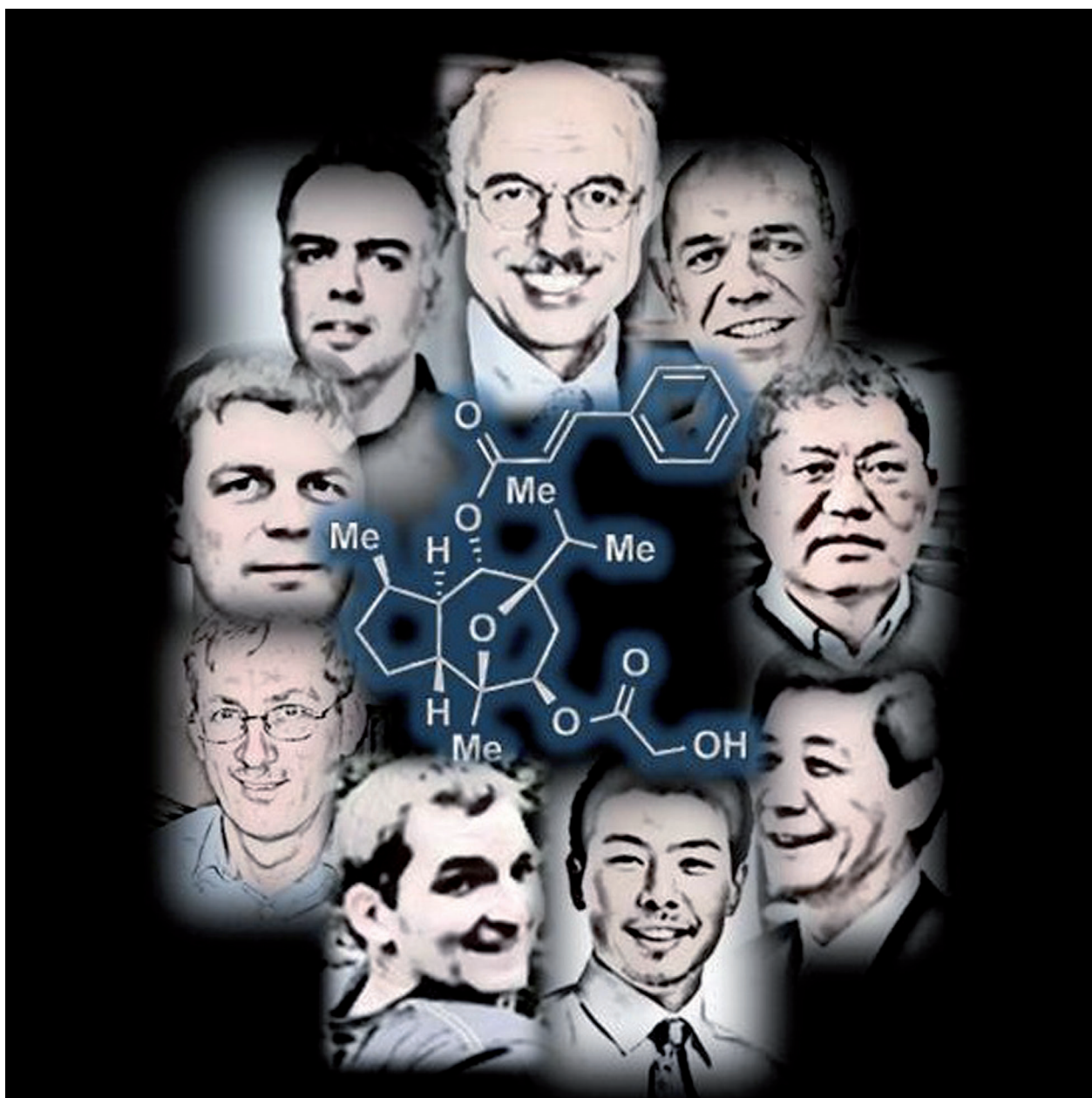


Chemical Synthesis of the Englerins

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Dedicated to Professor K. C. Nicolaou for his contribution to chemical education in Singapore and on the occasion of his 65th birthday



Abstract: In the long lasting battle against cancer, Nature sometimes gives a helping hand to researchers to find new drugs for the treatment of diseases and improvement of patients' well-being. Englerin A has emerged as a promising anticancer candidate as well as being an exciting synthetic challenge for organic chemists. This focus review

summarizes the total syntheses reported to date and the synthetic approaches toward analogues of this fascinating natural product.

Keywords: cancer • guaianolide • natural products • sesquiterpene • total synthesis

1. Introduction

1.1. Origin and Chemical Structure

With more than 50000 structures known to date, the terpenoids constitute the largest family of natural products. By definition, these secondary metabolites do not have any apparent function in connection with growth and development, but have been shown to play important roles in communication, defense, and many other functions.^[1] More profoundly, these natural products have been demonstrated to interact with biomolecules and, as such, represent privileged structures for the discovery of novel small-molecule medicines. Indeed, Nature has provided many exciting terpenes with remarkable structural diversity and therapeutic potential.^[2] Englerin A (**1**) and B (**2**), two closely related guaiane sesquiterpenoids, are amongst the most recent additions. They are characterized by a unique 5-6-5 tricyclic fused system in which two of the seven stereogenic centers are connected through an ether bridge (Figure 1).^[3] The potent and selective biological properties of englerin A (**1**), combined with the synthetic challenge presented by its densely functionalized polycyclic structure, immediately instigated interests from the synthetic community and beyond.

The purpose of this review is to highlight the syntheses of englerin A (**1**) and B (**2**) to date, and the preparation of selected analogues for structure–activity relationship investigations. In doing so, we hope to showcase the creative and elegant synthetic strategies developed, and inspire more advan-

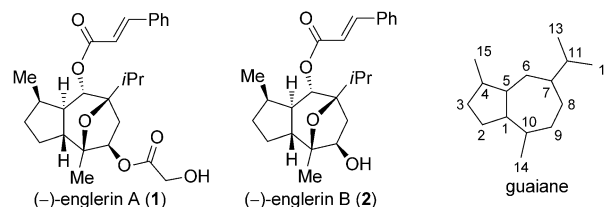


Figure 1. Molecular structures of (-)-englerin A (**1**) and B (**2**).

ces in the chemistry and biology of this fascinating molecule.

1.2. Isolation and Biological Activity

Phyllanthus engleri, native to south-eastern Africa, particularly Tanzania and Zimbabwe, is a plant of the Euphorbiaceae family that has found use in traditional medicines. The decoction of roots of this plant has been used for the treatment of ailments including epilepsy, stomach pain, and gonorrhoea; of note, its roots have been smoked to induce unconsciousness or death. The leaves and fruits are also used in the treatment of stomach pain. Prior to 2008, the triterpene phyllanthol was the only characterized compound isolated from *P. engleri*.^[4]

In a screen of natural product extracts against NCI-60, a panel of 60 diverse human cancer cell lines, 34 demonstrated selectivity for renal tumor cells over eight other organ panels. Of these 34, a CH₂Cl₂–MeOH extract of *P. engleri* was found to be highly selective and potent against the renal panel. Through a bioassay-guided fractionation of the stem bark extract and subsequent chromatography, englerin A was isolated and identified as the principal bioactive ingredient. A related structure lacking the C9 glycolic ester moiety, englerin B, was also isolated. Englerin A was found to inhibit the growth of renal cancer cell lines with remarkable potency and selectivity. Of the 8 renal lines in the NCI-60 cell panel, five cell lines were inhibited by englerin A with GI₅₀ values under 20 nM. The cytotoxicity of englerin A was significantly diminished in most other cell lines, with GI₅₀ values generally between 10 and 20 μM. Interestingly, englerin B was significantly less selective and less active in the same renal cell lines, while englerin B acetate displayed a 400-fold selectivity against the renal cell lines in a two-cell assay. Although glycolic acid is known to induce acute renal toxicity, other glycolic acid-containing natural products, such as saframycin R and pleuromutilin, failed to elicit selective

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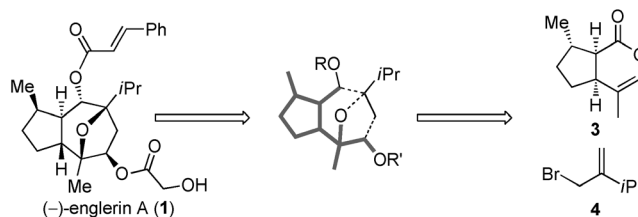
cytotoxicity in renal cancer cell lines.^[4] These findings suggest that while the C9 glycolic ester may not be critical for the selectivity and cytotoxicity of englerin A, it is an important structural element.^[5]

2. Total Syntheses of Englerin A and B, and their Analogues

2.1. Christmann's Total Synthesis of (+)- and (-)-Englerin A and B

Inspired by the promising biological activities of englerin A and the hypothesized biosynthetic pathway for the formation of the ether bridge through a transannular epoxide-opening,^[6] Christmann and co-workers reported the first synthesis of the englerins.^[7] Retrosynthetic analysis revealed that the core structure of the natural product could be obtained from the readily available *cis/trans* nepetalactone **3** and the six-carbon fragment **4** (Scheme 1).

The absolute configuration of englerin A was undetermined at the outset of Christmann's study. As such, their



Scheme 1. Christmann's synthetic strategy towards englerin A (1).

synthesis commenced with an *m*-CPBA-mediated epoxidation (*m*-CPBA = *meta*-chloroperoxybenzoic acid) of an arbitrarily chosen (+)-*cis/trans* nepetalactone **3** to afford a 1:1.5 mixture of epoxy lactones **5** and **6** in 91% yield. Treatment of the epoxy lactone **6** under methanolysis conditions provided the ring-contracted formyl lactone **8** (93%) through the intermediate alkoxyformyl ester **7**. A Barbier-type addition of organozinc species **9**, generated in situ from zinc dust and allyl bromide **4** under sonication conditions, smoothly delivered homoallylic alcohol **10** (93%, d.r.=5:1), which was subsequently reduced through the action of LiAlH₄ to afford triol **11** in 98% yield. Protection of the vicinal diol



Rebecca Pouwer was born in 1982 in Brisbane, Australia. After receiving her B.Sc. (Hons) and Ph.D. from the University of Queensland under the guidance of Dr. Craig M. Williams, she undertook postdoctoral studies at Imperial College London under the guidance of Dr. D. Christopher Braddock. In 2010, Rebecca commenced further postdoctoral studies under the guidance of Dr. David Y.-K. Chen at the Chemical Synthesis Laboratory (CSL) at Biopolis under the Agency for Science, Technology and Research (A*Star), Singapore, where she studied

the total synthesis of complex natural products. Rebecca is currently a Research Fellow at the Eskitis Institute for Cell and Molecular Therapies, Australia.



Jean-Alexandre Richard was born in 1982 in Tours, France. He studied at the University of Tours, Le Havre and Rouen where he obtained his Ph.D. in 2008 under the supervision of Professor Pierre-Yves Renard and Dr. Anthony Romieu, working on the development of luminescent probes for molecular imaging. Since 2009 he has been working as a Research Scientist at the Institute of Chemical and Engineering Sciences (ICES), under the Agency for Science, Technology and Research (A*Star), Singapore, focusing his research on the total synthesis of natural products and the development of new synthetic methodologies.



Chih-Chung Tseng was born in 1977 in Pingtung county, Taiwan. He began his tertiary education at the National Cheng Kung University (Tainan City, Taiwan), and was awarded with B.Sc. and M.Sc. degrees in 2000 and 2002, respectively. Upon the completion of national service, he worked as a Research Assistant at the Genomics Research Center (GRC) of Academia Sinica (Taipei, Taiwan). In 2005, he commenced his doctoral studies under the supervision of Professor Alan C. Spivey at Imperial College London (UK) on the synthesis of bioactive compounds using germanium chemistry. After postdoctoral work under the

guidance of Dr. David Yu-Kai Chen, in 2011, he was appointed as an Assistant Research Fellow at the Department of Applied Chemistry, National Chiao Tung University, Taiwan.

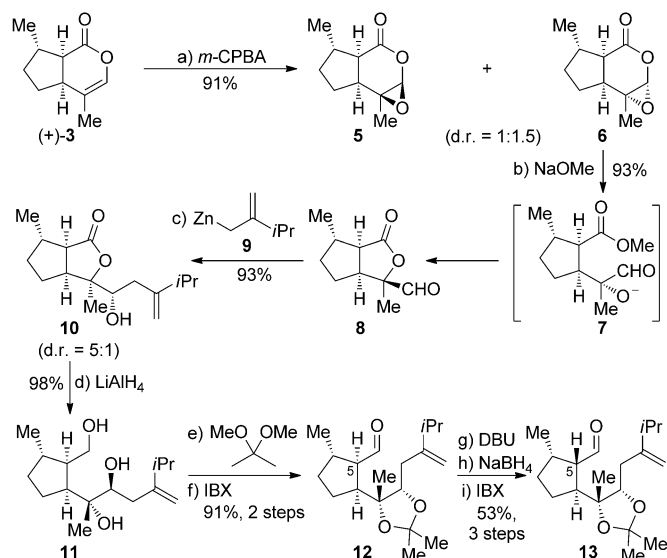


David Yu-Kai Chen was born in 1976 in Taipei, Taiwan. After receiving a B.Sc. degree (Hon) from the University of Auckland in 1998 and a Ph.D. from the University of Cambridge in 2001 under the guidance of Professor Ian Paterson, he pursued postdoctoral work under the guidance of Professor K. C. Nicolaou at The Scripps Research Institute. After a short stay at the Merck Research Laboratory at Rahway, New Jersey, he was appointed as the Principal Investigator of the Chemical Synthesis Laboratory (CSL) at Biopolis in 2005, under the Agency for

Science, Technology and Research (A*Star), Singapore. In 2011, he relocated his research operation to Seoul, South Korea, where he was appointed as Professor of Organic Chemistry at Seoul National University. Dr. Chen's research interests focus on the discovery and development of new synthetic strategies and technologies, total syntheses of bioactive natural products, and chemical biology.

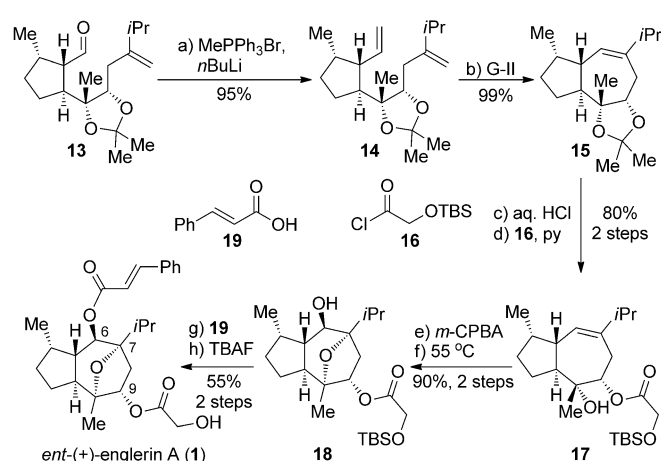
and oxidation state adjustment provided aldehyde **12**; epimerization of its C5 stereocenter with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature led to an inseparable mixture (ca. 3:1) of epimers. Reduction of the aldehyde into the corresponding primary alcohol with NaBH₄ allowed for clean separation of the two diastereomers of which the major isomer was re-oxidized upon treatment with 2-iodoxybenzoic acid (IBX) to give the desired stereoisomer **13** in 53% yield over the three steps (Scheme 2).

Next, Wittig olefination of aldehyde **13** followed by ring-



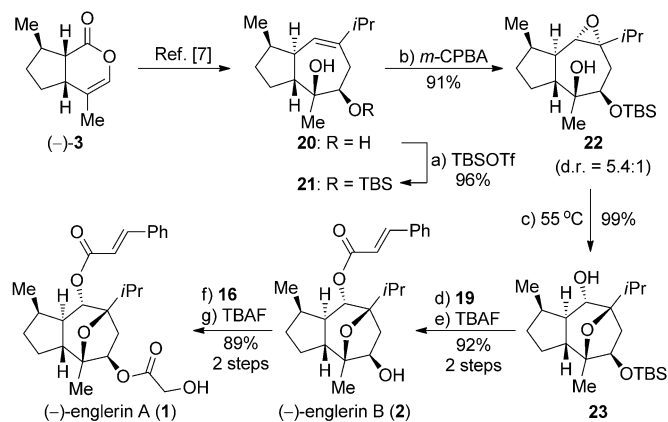
Scheme 2. Synthesis of aldehyde **13** through a base-mediated ring contraction and Barbier-type addition.^[7]

closing metathesis^[8] (Grubbs second-generation catalyst, G-II)^[9] of the resulting diene **14** furnished guaiane **15** with remarkable efficiency (99%). Acid-mediated hydrolysis of the ketal moiety followed by selective esterification of the resulting secondary hydroxy group with *tert*-butyldimethylsilyl (TBS)-protected glycolic acid chloride **16** provided the protected glycolate ester **17** in 80% overall yield. Upon epoxidation of **17** with *m*-CPBA (d.r. = 2.3:1), the crucial transannular epoxide opening to establish the ether bridge of englerin A was found to proceed slowly at room temperature. Alternatively, heating the reaction mixture at 55 °C promoted quantitative conversion and provided secondary alcohol **18** in 90% overall yield. After Yamaguchi esterification^[10] of alcohol **18** with cinnamic acid **19** and desilylation with tetrabutylammonium fluoride (TBAF), at last, englerin A (**1**) was secured in 55% yield. Spectroscopic data for the synthetic compound concurred with the reported assignment for the isolated compound, with the exception that the optical rotation was found to be of the opposite sign to the naturally occurring substance. Therefore, the absolute configuration of the synthetic material was assigned as *ent*-(+)-englerin A (**1**) (Scheme 3).



Scheme 3. Ring-closing metathesis and transannular epoxide opening strategy for the total synthesis of *ent*-(+)-englerin A.^[7]

Christmann and co-workers subsequently reported a more practical synthetic route towards (–)-englerin A (**1**) and B (**2**) based on an improvement of their first-generation approach.^[5b] This second-generation synthesis started from (–)-*cis/trans* nepetalactone **3** in accordance with the previously developed chemistry. Epoxidation of mono-TBS ether **21** led to a significant improvement in diastereoselectivity in favor of the desired diastereoisomer (d.r. = 5.4:1 cf. 2.3:1 in the first-generation approach). Transannular epoxide opening of **22** proceeded smoothly to give secondary alcohol **23** in excellent yield. (–)-Englerin B (**2**) was subsequently prepared by an esterification of the resulting alcohol **23** with cinnamic acid **19** under Yamaguchi conditions, followed by deprotection of the TBS ether (TBAF). Their synthetic efforts concluded with the installation of a TBS-protected glycolate ester subunit and desilylation to afford (–)-englerin A (**1**) in 89% yield over the two steps (Scheme 4). Furthermore, by using this synthetic sequence, a number of englerin analogues with variation at the C7 alkyl and C6/C9 ester side chains were readily prepared for biological evaluation.

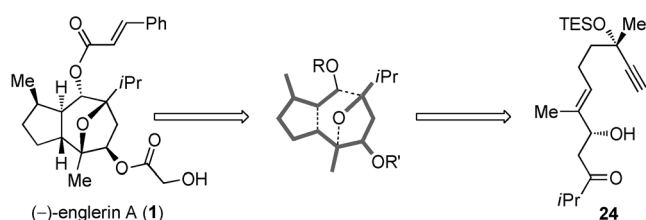


Scheme 4. Second-generation synthetic route for the total synthesis of (–)-englerin A and analogues.^[5b]

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2.2. Echavarren's Total Synthesis of (–)-Englerin A and B

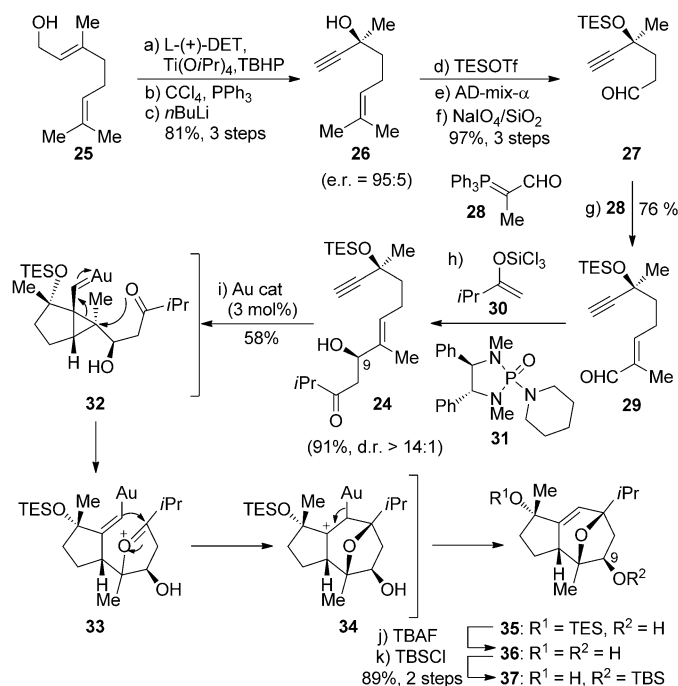
Echavarren and co-workers reported an exquisite and straightforward synthetic sequence towards (–)-englerin A^[11] that featured a Au-catalyzed cycloisomerization^[12] to construct the guaiane sesquiterpene scaffold from a linear precursor (**24**, Scheme 5).^[13]



Scheme 5. Echavarren's cycloisomerization strategy for the total synthesis of (–)-englerin A.

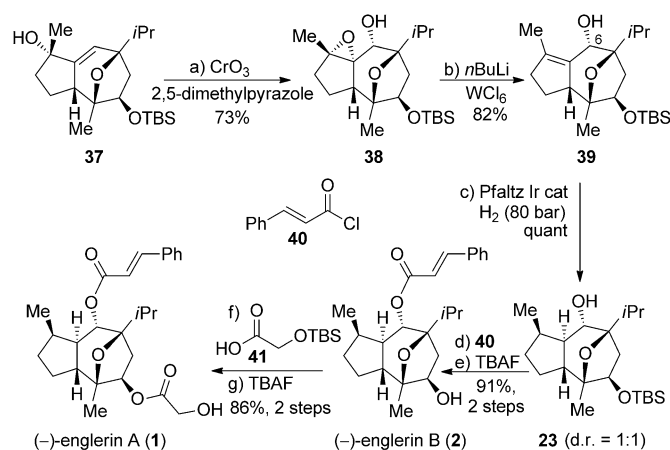
In this context, Echavarren's synthesis commenced with the preparation of known 1,6-enyne **26** through a three-step sequence that involved a Sharpless asymmetric epoxidation^[14] and an Appel reaction^[15] of the resulting epoxy alcohol, followed by treatment with *n*BuLi to install the terminal alkyne (81% yield, over 3 steps, e.r.=95:5). Subsequent protection of the propargylic alcohol **26** as its triethylsilyl (TES) ether followed by Sharpless asymmetric dihydroxylation^[16] and oxidative cleavage of the vicinal diol (NaIO₄/SiO₂) gave aldehyde **27** in 97% overall yield. Wittig olefination of aldehyde **27** with ylide **28** afforded enal **29** stereoselectively. The latter compound was subsequently subjected to a Denmark aldol reaction with trichlorosilyl enol ether **30** in the presence of chiral phosphoramidate catalyst **31**^[17] to furnish **24** in 91% yield and d.r. > 14:1. The crucial Au^I-catalyzed cycloisomerization reaction was investigated systematically, where the choice of Au^I complexes and C9 hydroxy-protecting groups were examined. Preliminary studies using hydroxy-protected derivatives gave inferior results. However, the anticipated cycloisomerization process was found to proceed smoothly upon treatment of free hydroxy enyne **24** with [IPrAuNCPPh]SbF₆,^[18] presumably through the gold carbene intermediate **32**, to afford tricyclic alcohol **35** in 58% yield. Further protecting group manipulations of tricycle **35** furnished allylic alcohol **37** in 89% overall yield (Scheme 6).

To complete the synthesis, epoxy alcohol **38** was first obtained from a CrO₃·(2,5-dimethylpyrazole) complex-mediated oxidative rearrangement of allylic alcohol **37**,^[19] and subsequently converted into alcohol **39** under the influence of WCl₆ and *n*BuLi.^[20] With the C6 hydroxy group suitably positioned, it was anticipated that hydroxy-directed hydrogenation^[21] of the trisubstituted alkene **39** would overcome the inherent facial bias of the substrate to selectively establish the *trans*-fused ring junction. In the event, hydrogenation of **39** with Pfaltz's iridium catalyst^[22] and H₂ (80 bar) at 23 °C afforded **23** in quantitative yield but as a separable 1:1 mixture, whereas Raney-Ni/H₂ conditions yielded exclusively the undesired stereoisomer. Advancing the synthesis for-



Scheme 6. Synthesis of the oxatricyclic core of englerin A through Au-catalyzed cycloisomerization.^[11] DET = diethyl tartrate.

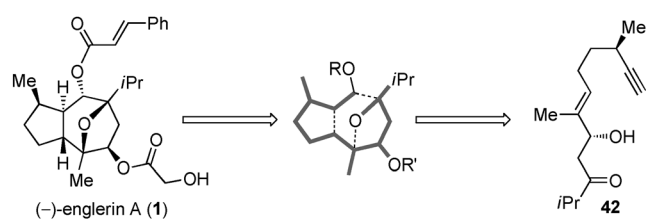
ward, hydrogenation product **23** was esterified with cinnamoyl chloride (**40**) and desilylated with TBAF to give englerin B (**2**) in a yield of 91% over both steps. A late-stage Yamaguchi esterification^[10] of englerin B (**2**) with TBS-protected glycolic acid (**41**) followed by removal of the primary TBS ether (AcOH-buffered TBAF) ultimately provided (–)-englerin A (**1**) in 86% overall yield (Scheme 7).



Scheme 7. Completion of the total synthesis of (–)-englerin A (**1**) and B (**2**).^[11]

2.3. Ma's Total Synthesis of (–)-Englerin A

Concurrently with Echavarren's group, Ma and co-workers reported a synthetic strategy^[11b,23] that shared the same concept as in Echavarren's study by employing an analogous

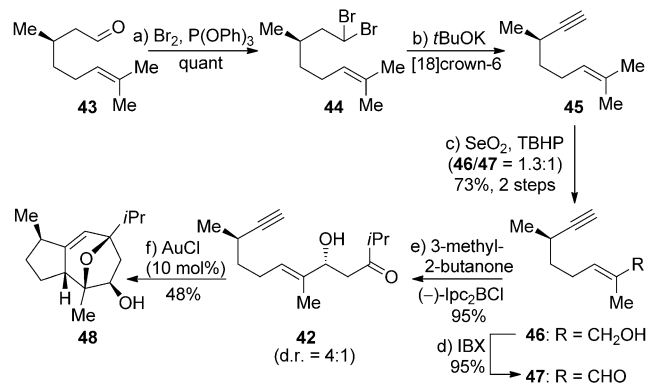


Scheme 8. Ma's cycloisomerization strategy towards the total synthesis of (-)-englerin A (1).

enyne precursor to establish the tricyclic framework through a Au-catalyzed cycloisomerization cascade (Scheme 8). Moreover, this developed route illustrated an example of a protecting-group-free synthesis of a complex natural product.^[24]

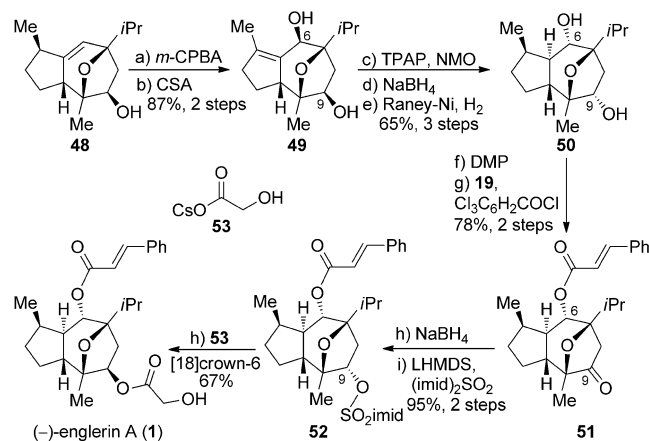
The readily available chiral starting material, (*R*)-citronellal (43), was converted into gem-dibromide 44 through the combined action of Br₂ and P(OPh)₃.^[25] Elimination of HBr from 44 under basic conditions (*t*BuOK) installed the terminal alkyne, which was subjected to a SeO₂-mediated allylic oxidation^[26] to afford a 1.3:1 mixture of allylic alcohol 46 and α,β -unsaturated aldehyde 47. The former (46) was rapidly oxidized with IBX^[27] to give the desired aldehyde 47 in 71% overall yield. Enantioselective boron-promoted aldol reaction between α,β -unsaturated aldehyde 47 and 3-methyl-2-butanone furnished β -hydroxy ketone 42 in excellent yield with a 4:1 ratio in favor of the desired diastereoisomer. In concurrence with Echavarren's results, the unprotected β -hydroxy ketone served as the most suitable substrate for the proposed Au-catalyzed reaction, to afford tricyclic alcohol 48 in 48% yield as a single diastereomer (Scheme 9).

To accomplish the remaining synthetic tasks, tricyclic alcohol 48 was first subjected to a two-step sequence that involved a *m*-CPBA-mediated epoxidation followed by an acid-promoted epoxide opening to yield diol 49 in 87% overall yield. The authors envisaged that the *trans*-fused ring system of englerin A could be prepared through a hydroxy-directed hydrogenation.^[21] To do so, the configura-



Scheme 9. Synthesis of key tricyclic alcohol 48 through Au-catalyzed cycloisomerization.^[23]

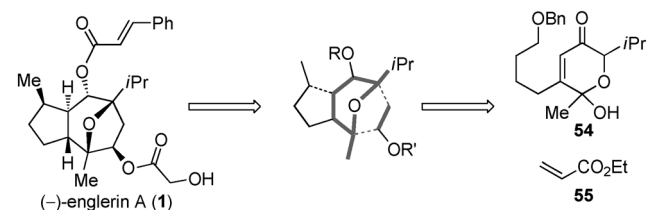
tions at C6 and C9 were inverted by an oxidation/reduction sequence (tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO)^[28] followed by NaBH₄). In stark contrast to Echavarren's results, hydrogenation of the resulting diol using Raney-Ni (H₂, 90 atm) at elevated temperature afforded the desired product 50 as a single diastereomer (65%, 3 steps). Regioselective functionalization of diol 50 was achieved by selective oxidation of the less-hindered C9 hydroxy group with Dess–Martin periodinane (DMP)^[29] followed by Yamaguchi esterification^[10] to install the C6 cinnamic ester, thereby affording ketone 51 in 78% overall yield. Finally, the C9 glycolate ester was introduced through NaBH₄ reduction followed by activation of the resulting secondary alcohol as its imidazolyl sulfonate 52 (95%, over 2 steps), and subsequent displacement of the C9 sulfonate with cesium glycolate (53) in the presence of crown ether [18]crown-6 to give (-)-englerin A (1) in 67% yield (Scheme 10).



Scheme 10. Protecting-group-free strategy to obtain (-)-englerin A.^[23] CSA = camphorsulfonic acid.

2.4. Nicolaou–Chen Total Synthesis of (±)-Englerin A and B

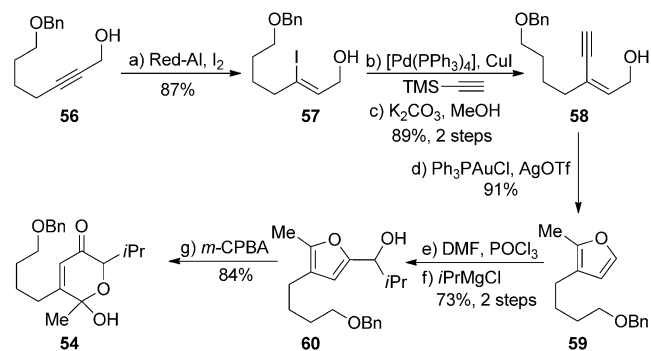
Shortly after the first total syntheses of englerin A (1) and B (2), Nicolaou, Chen and co-workers reported the first cycloaddition-based approach to these natural products from dihydropyranone precursor 54 and acrylate 55 (Scheme 11).^[30]



Scheme 11. Nicolaou–Chen bond disconnection towards englerin A and B.

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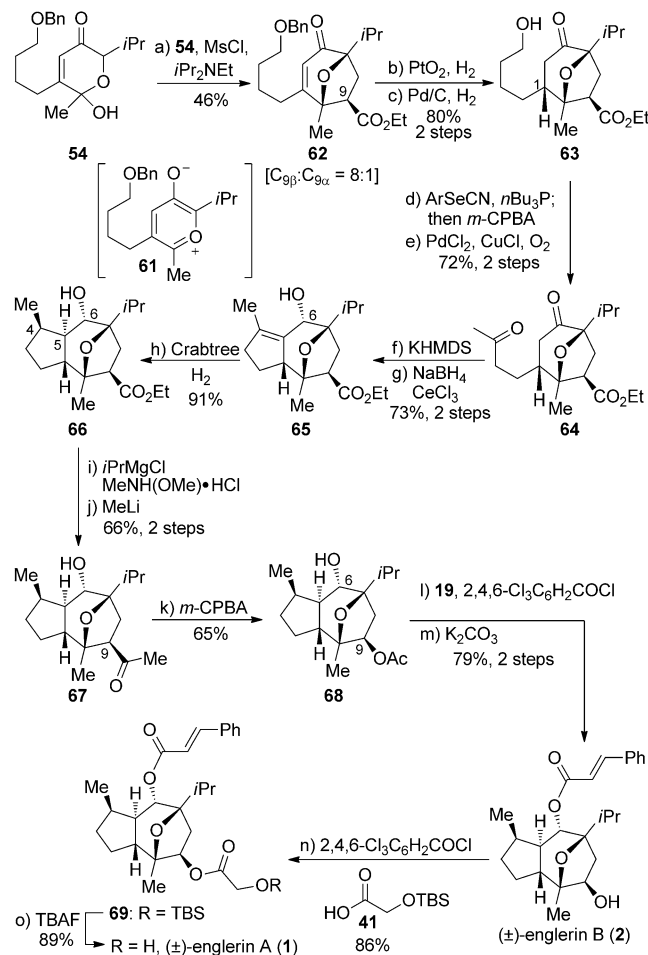
Starting from propargyl alcohol **56**, its reduction followed by iodination afforded iodoolefin **57** which underwent subsequent Sonogashira coupling to give alkyne **58** after desilylation. The Au-catalyzed formation of furan **59** proceeded smoothly^[31] and, after a Vilsmeier–Haack formylation, the isopropyl group of the englerins was introduced through the addition of isopropyl Grignard reagent to the intermediate aldehyde. Furan **60** was then engaged in an Achmatowicz rearrangement to provide dihydropyranone **54**,^[32] the key precursor for the proposed [5+2] cycloaddition (Scheme 12).



Scheme 12. Synthesis of the [5+2] cycloaddition precursor through a Au-catalyzed furan formation and Achmatowicz rearrangement.^[30] DMF = *N,N*-dimethylformamide.

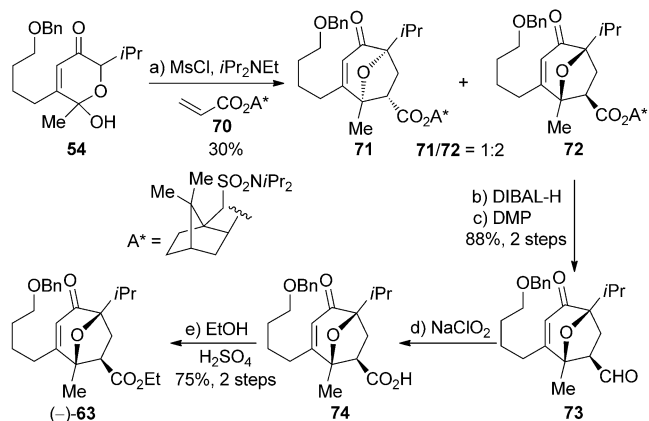
Through the combined action of mesyl chloride and diisopropylethylamine on dihydropyran **54**, the transient oxopyrylium species **61** was formed and participated in a [5+2] cycloaddition with ethyl acrylate to afford the oxygen bridged seven-membered ring **62** in a 8:1 ratio with respect to the configuration at C9.^[33] Next, a two-step hydrogenation allowed for the reduction of the double bond of enone **62** and the removal of the benzyl group to yield alcohol **63** in 80% overall yield. This primary alcohol was then transformed into a terminal olefin through selenium chemistry (ArSeCN/*n*Bu₃P, then *m*-CPBA),^[34] and the resulting alkene was subjected to a Wacker oxidation^[35] to give methyl ketone **64** in 72% overall yield. Formation of the five-membered ring by a potassium hexamethyldisilazide (KHMDS)-mediated aldol condensation generated the corresponding enone, and subsequent Luche reduction^[36] afforded **65** as a single isomer and in 73% overall yield. The trisubstituted olefin of **65** was then reduced by using a hydroxy-directed hydrogenation^[21] with Crabtree's catalyst^[37] to afford **66**. At this juncture, all that remained for the synthesis of englerin A (**1**) was the transformation of the C9 ester group into a hydroxy group, and introduction of the cinnamic and glycolic ester side chains. With these objectives in mind, the ester group was transformed into the corresponding Weinreb amide,^[38] and subsequently treated with methyl lithium to provide methyl ketone **67** in 66% overall yield. A Baeyer–Villiger oxidation of **67**^[39] then introduced the desired secondary alcohol as an acetoxy group. Introduction of the C6 cinnamic ester side chain was accomplished through a Yamaguchi esterification^[10] with cinnamic acid (**19**), and subse-

quent selective hydrolysis of the acetate group (K₂CO₃) provided englerin B (**2**) in 79% over the two steps. A second Yamaguchi esterification in the presence of acid **41** followed by desilylation ultimately provided (±)-englerin A (**1**) (Scheme 13).



Scheme 13. [5+2] cycloaddition strategy for the total synthesis of (±)-englerin A and B.^[30]

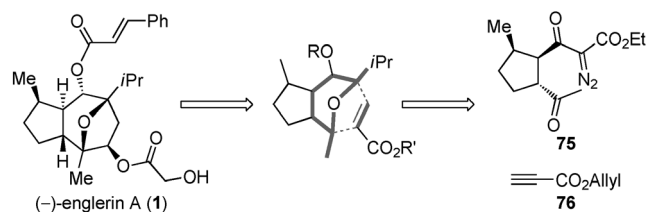
As an extension of this strategy, the group also completed a formal asymmetric synthesis of the englerins using the camphor-derived acrylate **70** as a chiral cycloaddition partner.^[40] The cycloaddition proceeded in a 30% (unoptimized) yield to afford cycloadducts **71** and **72** as a separable 1:2 mixture. Diisobutylaluminum hydride (DIBAL-H) reduction of **72** followed by reoxidation afforded aldehyde **73** in 88% overall yield. Enone (–)-**63**, a chiral intermediate analogous to its racemic counterpart (Scheme 13), was intercepted after two additional steps (Pinnick oxidation and Fischer esterification), thus completing a formal asymmetric synthesis of englerin A (**1**) and B (**2**) (Scheme 14).



Scheme 14. Chiral auxiliary-based [5+2] cycloaddition leading to enantiopure (-)-63 towards the total synthesis of (-)-englerin A and B.^[30]

2.5. Maier's Synthetic Approach Toward the Guaiene Core of the Englerins

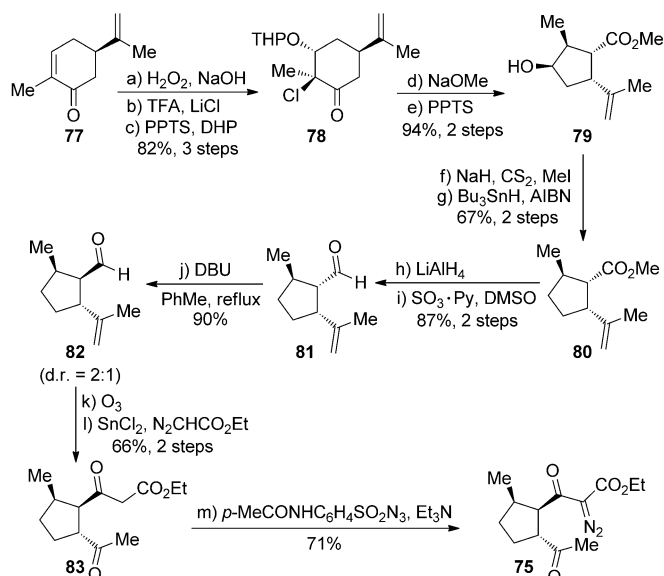
The efforts of Maier and co-workers towards the synthesis of englerin A called for a conceptually similar strategy to that described by Nicolaou, Chen et al.^[41] The key step of the overall synthetic strategy called for a [5+2] cycloaddition of a carbonyl ylide and a propiolate dipolarophile (Scheme 15).^[42]



Scheme 15. Maier's bond disconnection towards englerin A and B.

A chiral pool approach allowed for ready access to gram quantities of the cycloaddition precursor **75**, with (-)-carvone (**77**) serving as the source of enantiopure starting material. In the event, epoxidation of the enone moiety of **77** was followed by a regioselective opening of the resulting epoxide with a chloride (LiCl), and the so obtained secondary alcohol was protected with as a tetrahydropyranyl (THP) ketal (82% yield, three steps). Favorskii rearrangement^[43] of **78** induced a ring contraction to produce a cyclopentanecarboxylate intermediate, which, after THP deprotection, afforded alcohol **79** in 94% yield over the two steps. Barton–McCombie deoxygenation (67%, two steps)^[44] followed by a reduction/oxidation/epimerization sequence provided aldehyde **82** (2:1 ratio in favor of **82** over **81**), and finally, ozonolysis of its alkene moiety followed by β -keto ester formation and a diazo-transfer reaction delivered the key cycloaddition precursor **75** (47%, three steps, Scheme 16).

Upon heating a mixture of diazo compound **75**, allyl propiolate, and a trace amount of $[\text{Rh}_2(\text{OAc})_4]$ (1 mol%) at 100 °C for 15 minutes, cycloadduct **85** was smoothly formed

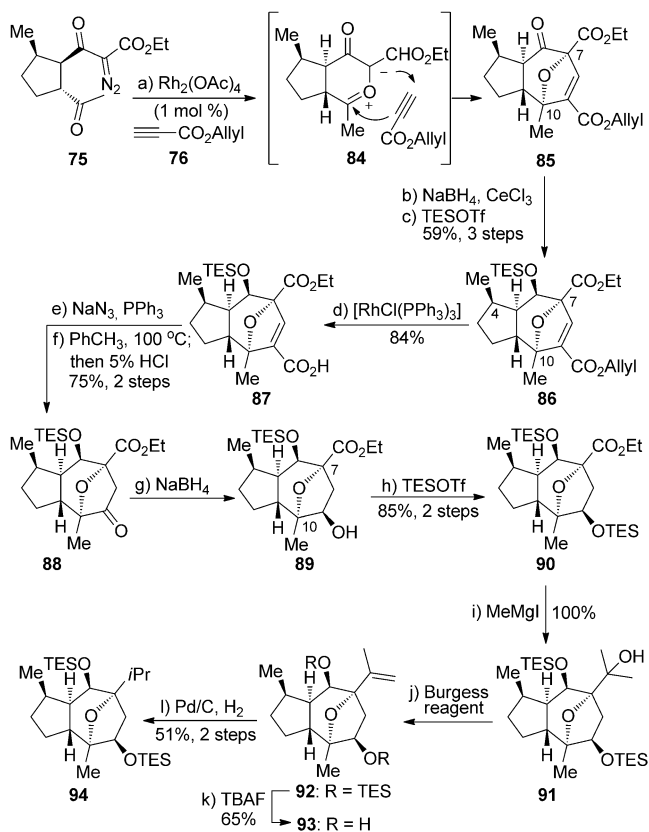


Scheme 16. Approach to optically active [5+2] cycloaddition precursor **75** from (-)-carvone (**77**).^[41] PPTS = pyridinium 4-toluenesulfonate; DHP = dihydropyran; AIBN = azobisisobutyronitrile.

but was found to be prone to epimerization. As such, the ketone functionality within **85** was immediately reduced (NaBH_4) and protected as a TES-ether (59% overall yield from **75**). Continuing the synthesis, the allyl ester was cleaved in the presence of a catalytic amount of Wilkinson catalyst $[\text{RhCl}(\text{PPh}_3)_3]$, and a subsequent Curtius rearrangement^[45] provided ketone **88** in 75% overall yield.

Next, reduction of ketone **88** with NaBH_4 into the corresponding alcohol **89** allowed for Maier and co-workers to determine the relative configuration of the tricyclic system through NOE studies. As a result, it was discovered that the cycloaddition had produced the undesired relative configuration at C7 and C10, thereby placing the oxygen bridge on the opposite face of the molecule with respect to the C4 methyl group. Despite this undesired outcome, further synthetic transformations on **89** were carried out to access a material that is structurally more closely related to the natural product. Initial TES-protection of **89** was followed by exhaustive methyl lithium addition to the ester functionality, thus leading to tertiary alcohol **91**. As radical deoxygenation was not effective for conversion of **91** into **94**, an alternative elimination–hydrogenation sequence (51%, two steps) was adopted to afford an advanced intermediate (**94**) that resembled the core structure of englerin A. Through this synthetic sequence, diol **93** was isolated and its X-ray analysis confirmed that the [5+2] cycloaddition had indeed occurred with the undesired facial selectivity. Although this synthetic route did not result in a total synthesis of englerin A, it did produce a novel analogue of the natural product and showcased an insightful chemical strategy for accessing the challenging guaiene core structure (Scheme 17).

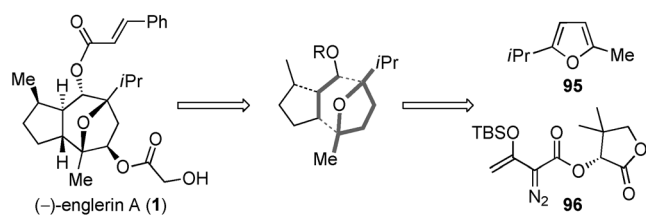
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Scheme 17. Rh-catalyzed [5+2] cycloaddition approach towards the guaiane skeleton of the englerins.^[41]

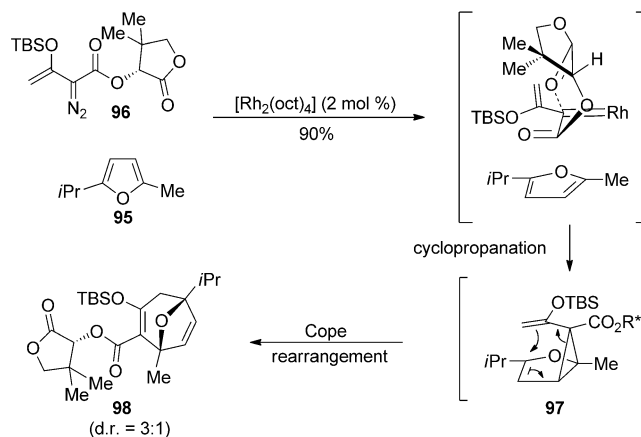
2.6. Theodorakis' Formal Synthesis of (–)-Englerin A

Inspired by the chemistry reported by Davies and co-workers,^[46] Theodorakis et al.^[47] implemented an enantioselective [4+3] cycloaddition to construct the oxygen-bridged seven-membered ring of englerin A, which culminated in a formal synthesis of the natural product (Scheme 18).



Scheme 18. Theodorakis' bond disconnection towards (–)-englerin A.

In this context, on exposure of a mixture of furan **95** and diazo compound **96** to a catalytic amount of $[\text{Rh}_2(\text{oct})_4]$, cycloadduct **98** was formed in 90% yield in a d.r. of 3:1. The origin of the selectivity, as reported by Davies and co-workers, is presented in Scheme 19. It was proposed that the asymmetric induction could be due to an interaction between the carbonyl group of the auxiliary and the rhodium carbenoid. This interaction would allow for efficient transfer



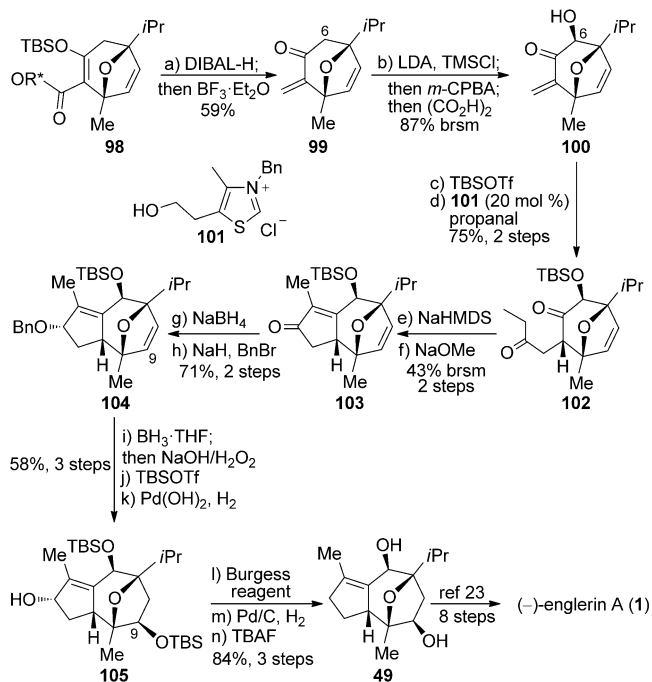
Scheme 19. Asymmetric [4+3] cycloaddition through a cyclopropanation/Cope rearrangement cascade.^[46]

of the asymmetric information from the auxiliary to the carbenoid position. The facial selective cyclopropanation followed by a Cope rearrangement then afforded the desired seven-membered oxabicyclic **98**.

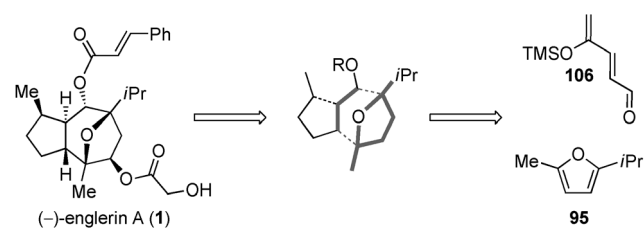
Next, removal of the chiral auxiliary with DIBAL-H was followed by a Lewis acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) induced elimination of the resulting β -hydroxy enol ether to yield enone **99** in 59% yield. A Rubottom oxidation (lithium *N,N*-diisopropylamide (LDA)/TMSCl, then *m*-CPBA)^[48] allowed for the introduction of the requisite C6 alcohol within the seven-membered ring. Homoallylic alcohol **100** was then protected as its TBS ether, and a Stetter reaction^[49] with propanal in the presence of thiazolium salt **101** allowed for the introduction of a side chain ready for the subsequent formation of the five-membered ring through an aldol condensation (NaHMDS , then NaOMe). A 1,2-reduction of enone **103** (NaBH_4) and protection of the resulting allylic alcohol as its benzyl ether (71%, 2 steps) was followed by a second oxygenation of the seven-membered ring through a stereoselective and regioselective hydroboration ($\text{BH}_3 \cdot \text{THF}$). After TBS protection of the secondary alcohol and removal of the benzyl ether (58% overall yield from **104**), the obtained alcohol **105** was eliminated through the action of Burgess reagent^[50] to afford a diene that, in turn, was selectively hydrogenated. Global deprotection then provided diol **49**, a previously reported intermediate in the total synthesis of englerin A reported by Ma and co-workers (Scheme 10). Thus, the sequence described by Theodorakis and co-workers constitutes a formal synthesis of the natural product (Scheme 20).

2.7. Lin's Synthetic Approach Toward the Guaiane Core of the Englerins

During their campaign towards the synthesis of englerin A (**1**), Lin and co-workers took advantage of an organocatalytic [4+3] cycloaddition reaction developed previously by Harmata et al.^[51] In doing so, the group reported the first application of this underutilized reaction in the context of a target-oriented synthesis (Scheme 21).^[52]



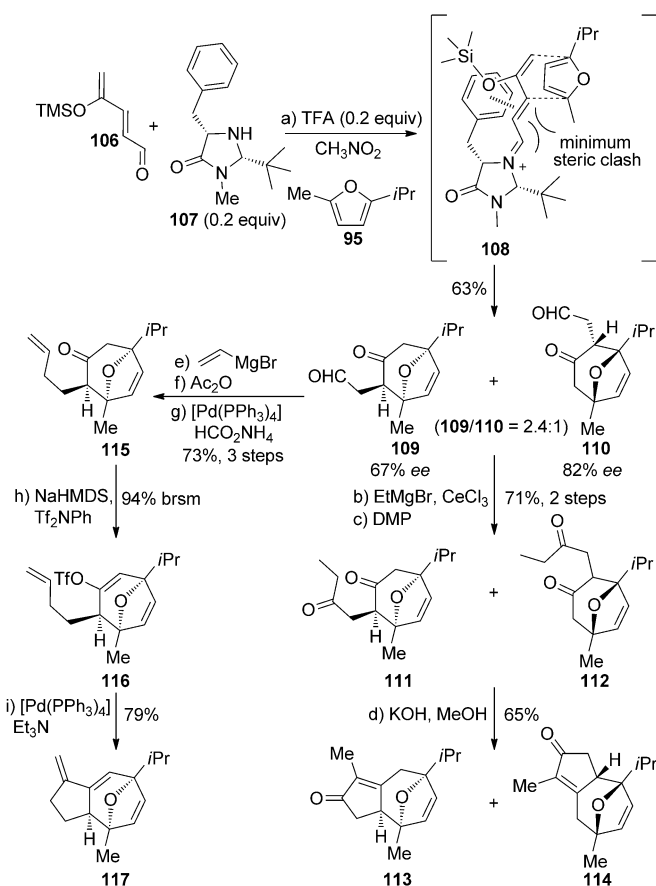
Scheme 20. Theodorakis' [4+3] cycloaddition strategy for the formal synthesis of (-)-englerin A.^[46]



Scheme 21. Lin's bond disconnection towards englerin A and B.

In the event, exposure of aldehyde **106** to MacMillan's catalyst **107**^[53] and trifluoroacetic acid (TFA) allowed for the formation of an iminium intermediate **108**, which underwent a reaction with furan **95** to afford a mixture of cycloadducts **109** and **110** in a combined yield of 63%. The nature of the solvent proved to be critical to the success of the reaction, and the use of nitromethane was found to offer the best reaction rate and yield. Lin et al. rationalized the enantioselectivities of the products (67% *ee* for **109**, 82% *ee* for **110**) with model **108** in which the (*E*)-configuration of the iminium was stabilized through π - π interaction with the aromatic group, while the bulky *tert*-butyl group blocked one face of the diene. A moderate regioselectivity (**109**:**110** = 2.4:1) with regard to the furan moiety was observed, in which the major and desired product resulted from a minimized steric interaction with the bulky isopropyl group. It is worth noting that the absolute configuration of cycloadduct **109** is opposite to that of (-)-englerin A (**1**); thus, its further elaboration would lead to the enantiomer of the natural product.

Moving forward, the mixture of cycloadducts was advanced in two distinct routes to provide access to the guaiane core of englerin A (**1**). The first of these routes required the addition of ethylmagnesium bromide to aldehydes **109** and **110** followed by Dess–Martin periodinane (DMP) oxidation^[29] to provide diketones **111** and **112** (71% yield, 2 steps) which, under basic conditions (KOH, MeOH), afforded enones **113** and **114** in 65% yield. Alternatively, aldehydes **109** and **110** were subjected to a sequence that involved the addition of vinyl Grignard, acetylation of the so obtained allylic alcohol, and subsequent Pd-mediated reductive deacetoxylation through the intermediacy of a π -allyl species to generate **115** as a mixture of regioisomers. The isomers were separated at this stage, and subsequent formation of vinyl triflate **116** proceeded regioselectively on the less-substituted side of the ketone. The final operation of the sequence called for an intramolecular Heck reaction ([Pd(PPh₃)₄], Et₃N, 50°C), which proceeded exclusively in a 5-*exo*-trig fashion to provide bicycle **117** in 79% yield (Scheme 22).



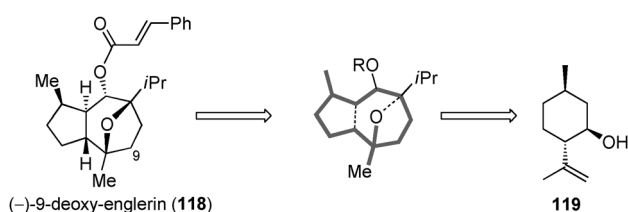
Scheme 22. Organocatalytic [4+3] cycloaddition approach towards the guaiane core of (+)-englerin A.^[51a]

2.8. Maier's Total Synthesis of (-)-9-Deoxy-englerin

Establishing structure–activity relationships through the biological evaluation of natural product analogues constitutes an important aspect of endeavors in total synthesis.^[54] Syn-

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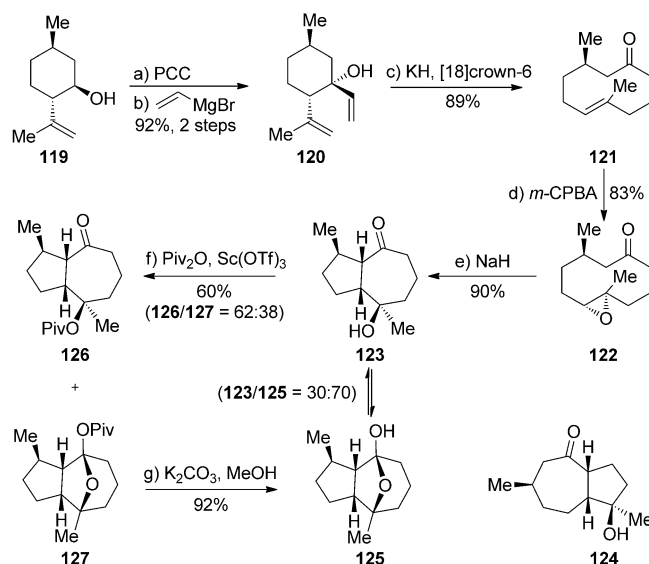
thetic strategies that allow for access to modified core structures are therefore of great importance, and it is for this reason that the Maier group developed a synthesis of (–)-9-deoxy-englerin (**119**).^[55] As previously discussed,^[5] Chen and co-workers reported in 2011 that the biological activity of englerin A analogues could be retained if the cinnamic acid moiety was moderately modified; by contrast, the modification of the C9 glycolic acid residue led to a significant loss of cytotoxicity. Maier's proposed synthesis of 9-deoxy-englerin would therefore allow for further confirmation of the latter structure–activity relationship, and in doing so offered a novel strategy for the synthesis of the guaiane core (Scheme 23).



Scheme 23. Maier's bond disconnection towards 9-deoxy-englerin (**118**).

Maier and co-workers envisaged a synthetic strategy that featured an intramolecular epoxide opening of a medium-sized ring to generate the annulated 5,7-bicyclic system, and a late-stage transannular ether formation to cast the oxo-bridge of the englerins. Commencing with (–)-isopulegol (**119**), oxidation and subsequent addition of vinylmagnesium bromide furnished **120** uneventfully in 92% yield. Allylic alcohol **120** was subsequently treated with potassium hydride to effect an anionic oxy-Cope rearrangement^[56] to give the ten-membered ring **121** in 89% yield. The macrocyclic *trans*-alkene was epoxidized through the action of *m*-CPBA to yield epoxide **122** as a single diastereomer (83%), the structure of which was confirmed by X-ray crystallography. With epoxide **122** in hand, the stage was set for regioselective transannular epoxide opening.^[6] Initial attempts to achieve this transformation led to a mixture of **123** and **124**, resulting from the nonselective formation and subsequent nucleophilic attack of the regioisomeric enolates. Optimization of this process eventually called for the treatment of **122** with sodium hydride at elevated temperature, after which the desired isomer **123** was obtained as a single regioisomer in 90% yield that existed in equilibrium with hemiacetal **125** (30:70 in CDCl₃). In the presence of pivalic anhydride and scandium triflate,^[57] formation of the esterified open form **126** was favored (**126**:**127** = 62:38), and was separated from **127** by column chromatography (Scheme 24).

Continuing from **126**, the C7 isopropenyl group was introduced by an aldol reaction with acetone, followed by elimination to furnish ketone **129** in 83% yield. At this point in the synthesis, epimerization of the C5 stereocenter to generate the *trans*-ring junction and migration of the terminal olefin of **129** to furnish the tetra-substituted alkene for the ensuing transannular etherification was necessary. Both op-



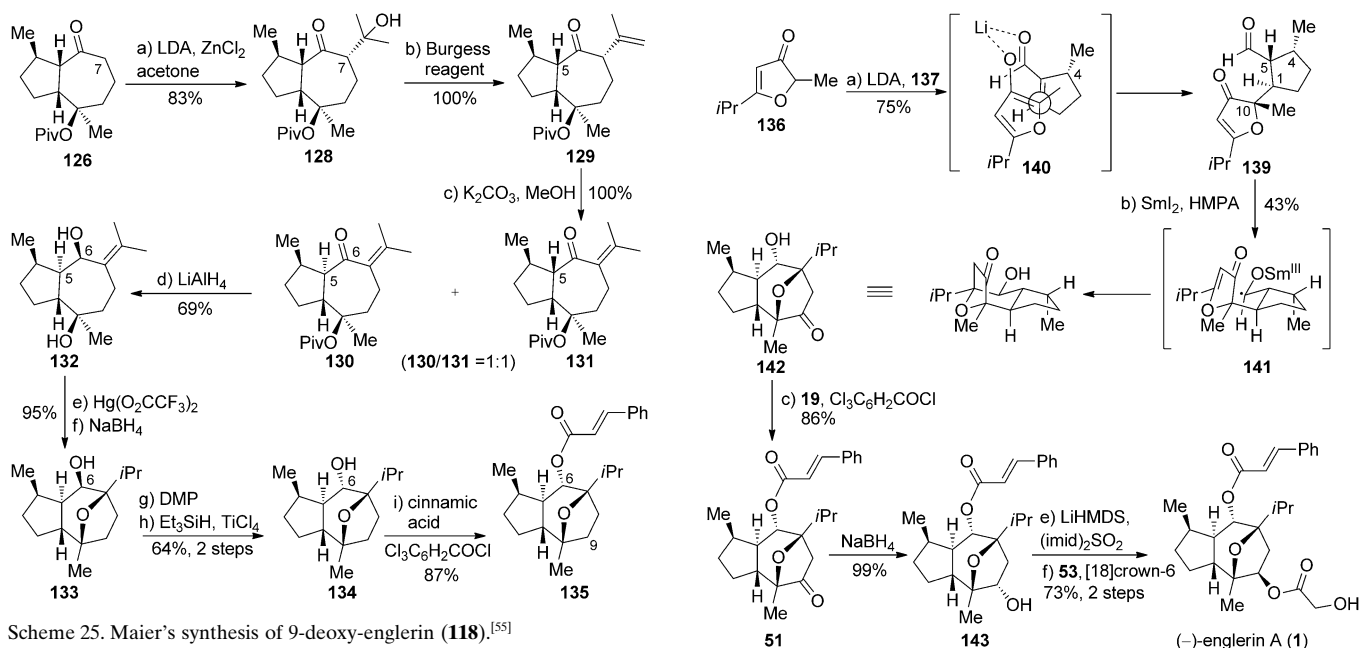
Scheme 24. Maier's transannular epoxide opening approach towards 9-deoxy-englerin (**118**).^[55]

erations were efficiently accomplished upon treatment of **129** with methanolic potassium carbonate, and **130** was isolated as a separable 1:1 mixture of C5 epimers in which the separated *cis* isomer (**131**) could be recycled through epimerization. Interestingly, the pivalic ester group was stable under these conditions, and was eventually removed upon treatment with LiAlH₄ with concomitant reduction of the C6 ketone to provide diol **132** in 69% yield.

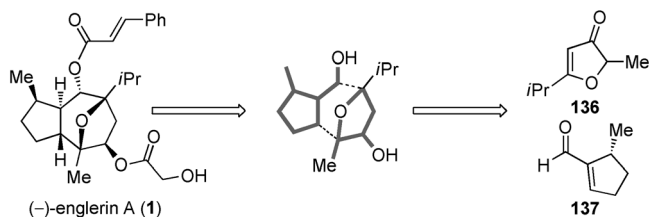
The transannular ether linkage was installed through a Hg^{II}-mediated oxymercuration/reduction sequence of alkene **132** to provide alcohol **133** in 95% yield. Other conditions to induce the transannular etherification, including treatment with acid or electrophilic selenium, were tried without success. At this stage, alcohol **133** differs from 9-deoxy-englerin (**135**) merely by the inversion and esterification of the C6 alcohol. Unfortunately, Maier and co-workers were not successful in their attempts to simultaneously invert the C6 center as its cinnamic ester under Mitsunobu conditions. They found, however, that a lengthier oxidation/reduction/esterification sequence produced 9-deoxy-englerin (**135**) in good yield. It is worth noting that the reduction of the ketone using conventional reagents (LiAlH₄, NaBH₄, L-selectride, DIBAL-H) only gave alcohol **133** so that an unusual condition using a silane (Et₃SiH) and a Lewis acid (TiCl₄) had to be employed to afford alcohol **134** with the desired stereochemistry (Scheme 25).^[58] The cytotoxic activity of **135** was evaluated against selected cell lines in comparison with (–)-englerin A (**1**). As expected from previous studies, **135** was in all cases less active than **1**, and most dramatically so for renal cancer cell lines.

2.9. Chain's Total Synthesis of (–)-Englerin A and B

The elegant synthesis of (–)-englerin A (**1**) and B (**2**) reported in 2011 by Chain and co-workers represents the most

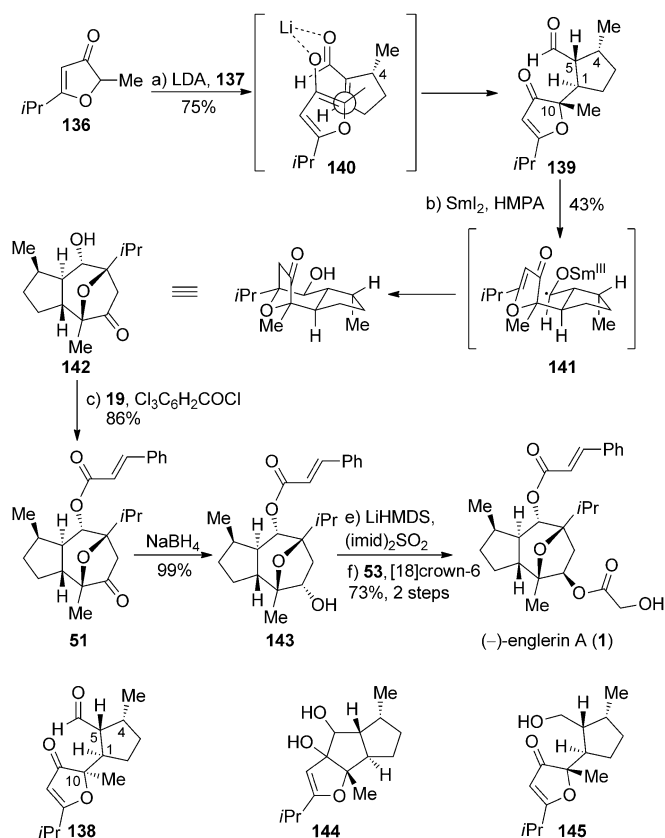
Scheme 25. Maier's synthesis of 9-deoxy-englerin (**118**).^[55]

concise synthesis published to date, and is a fine example of the power of an insightful retrosynthetic bond disconnection.^[59] This eight-step synthesis relied on carbonyl chemistry to construct the tricyclic core of englerin A (**1**) from **136** and **137** (Scheme 26).

Scheme 26. Chain's bond disconnection towards (-)-englerin A (**1**) and B (**2**).

The synthesis commenced with deprotonation of **136** at low temperature through the action of LDA, and subsequent Michael addition of the enolate to α,β -unsaturated aldehyde **137**. Aldehyde **139** was isolated in 75% yield as an inseparable 2:1 mixture in favor of the desired diastereomer **139** over other diastereomers. Thus, out of eight possible diastereomers, the relative configurations at C1, C4, C5, and C10 were set as desired in a remarkably efficient transformation.

Chain and co-workers proposed a model for the observed diastereoselection in which, through a chelated transition state (**140**), the C4 stereogenic center served as the directing element for the stereofacial selection (Scheme 27). This model was supported by the observation that the disruption of chelation with additives such as lithium chloride or hexamethylphosphoramide (HMPA) led to the preferential formation of **138**, which bears the opposite configuration at C10 (Scheme 27). From aldehyde **139**, the stage was set for

Scheme 27. Chain's total synthesis of (-)-englerin A (**1**).^[59]

construction of the tricyclic core of englerin A through an umpolung addition of the aliphatic aldehyde moiety to the proximal α,β -unsaturated ketone. Though many strategies are known in the literature to achieve this type of transformation, Chain and co-workers favored a reductive carbonyl-alkene cyclization approach through the application of samarium(II) iodide.^[60] Treatment of the diastereomeric mixture of **139** with SmI_2 in the presence of HMPA in THF yielded the desired compound **142** in 43% isolated yield (ca. 66% maximum yield based on the diastereomeric purity of **139**). In this transformation, the C6–C7 carbon–carbon bond of englerin A was forged diastereoselectively through the radical intermediate **141**. Thus, the core of englerin A (**1**) was constructed in only two steps from **136** and **137**. While the use of HMPA as an additive in the reaction was found to be essential, the effect of other additives on the SmI_2 -mediated reductive cyclization was also examined by the Chain research group. The addition of lithium chloride resulted in the formation of **144** through a pinacol-type coupling, whereas alcohol **145** was produced when the reaction was carried out in the presence of various proton sources (Scheme 27). Introduction of the cinnamic ester side chain was achieved uneventfully in 86% yield to provide compound **51**. As previously discussed, the synthesis of **51** was first described by Ma and co-workers (Scheme 10); therefore, Chain's synthesis of this intermediate constitutes a formal synthesis of englerin A. Nevertheless, Chain et al.

completed the synthesis utilizing Ma's reported conditions to afford englerin A (**1**) in three further synthetic steps, and in 20% overall yield from starting materials **136** and **137**. They further described the conversion of (–)-englerin A (**1**) into (–)-englerin B (**2**) through methanolic potassium carbonate hydrolysis of the glycolic ester.

Conclusions

The initial flurry of interest in the synthesis of this fascinating molecule has culminated in five total syntheses and one formal synthesis in the short time span since its isolation.^[61] As described, these syntheses have expanded the realms of possibility in the field, and stand as exemplars of elegance and evolution in synthetic strategy. Rightfully, interest in the synthesis of derivatives and analogues of englerin A (**1**) for the development of detailed structure–activity relationships and the elucidation of its mechanism(s) remains strong. The authors hope that this review will inspire further contributions in this area and trust that the noteworthy biological activity of englerin A (**1**) will soon be further understood and exploited.

Acknowledgements

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