Instructions for use

Title

Asymmetric Total Synthesis of (-)-Englerin A through Catalytic Diastereo- and Enantioselective Carbonyl Ylide Cycloaddition

Author(s)

Hanari, Taiki; Shimada, Naoyuki; Kurosaki, Yasunobu; Thrimurtulu, Neetipalli; Nambu, Hisanori; Anada, Masahiro; Hashimoto, Shunichi

Citation

Chemistry-A European journal, 21(33): 11671-11676

Issue Date

2015-08-10

Doc URL

http://hdl.handle.net/2115/62685

Rights

This is the accepted version of the following article: Hanari, T., Shimada, N., Kurosaki, Y., Thrimurtulu, N., Nambu, H., Anada, M. and Hashimoto, S. (2015), Asymmetric Total Synthesis of (-)-Englerin A through Catalytic Diastereo- and Enantioselective Carbonyl Ylide Cycloaddition. Chem. Eur. J., 21: 11671-11676, which has been published in final form at http://dx.doi.org/10.1002/chem.201502009

Type

article (author version)

File Information

manuscript.pdf

Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP
Asymmetric Total Synthesis of (−)-Englerin A through Catalytic Diastereo- and Enantioselective Carbonyl Ylide Cycloaddition


Abstract: An asymmetric total synthesis of the guaiane sesquiterpene (−)-englerin A, a potent and selective inhibitor of the growth of renal cancer cell lines, was accomplished. The basis of the approach is a highly diastereo- and enantioselective carbonyl ylide cycloaddition with an ethyl vinyl ether dipolarophile under catalysis by dirhodium(II) tetrakis[N-tetrachlorophthaloyl-(S)-tert-leucinate], [Rh₂(S-TCPTTL)₄], to construct the oxabicyclo[3.2.1]octane framework with concomitant introduction of the oxygen substituent at C9 on the exo-face. Another notable feature of the synthesis is ruthenium tetraoxide-catalyzed chemoselective oxidative conversion of C9 ethyl ether to C9 acetate.

(−)-Englerin A (1) (Figure 1), a guaiane sesquiterpene isolated from the stem bark of the East African plant Phyllanthus engleri by Beutler et al.,[1] was found to possess very potent growth inhibitory (GI) activity (GIₕ₀ < 20 nM) against four of eight renal cancer cell lines with approximately 1000-fold selectivity over most other cancer cell lines in the NCI-60 panel.[1] While the mechanism of action of englerin A remains to be elucidated.[2] It has very recently been disclosed that 1 activates transient receptor potential canonical channels 4 and 5 (TRPC4/5) in renal cancer cells to induce cell death caused by Ca²⁺ overload.[3] Structurally, this molecule features an oxygen-bridged 5-6-5 tricyclic system with seven contiguous stereogenic centers containing a cinnamate side chain at C6 and a glycolate fragment at C9 (englerin numbering). Not surprisingly, its great potential as a new drug lead in renal cancer chemotherapy coupled with a substantial structural challenge has rendered englerin A (1) a highly attractive target for synthetic investigations.[4] In 2009, Christmann et al. accomplished the first total synthesis of (−)-englerin A from (+)-trans,cis-neptetalactone utilizing an epoxylactone rearrangement, a stereoselective Barbier-type alkylation, a ring-closing metathesis, and a transannular epoxide opening as the key steps, thereby establishing the previously unknown absolute configuration of natural (−)-englerin A as shown in 1.[5] Since then, eight total syntheses,[6] three formal syntheses,[7] and several synthetic studies,[8] which are all based on innovative strategies and tactics, as well as results of structure-activity relationship studies,[9b,6c,7c,9] have been reported.

![Figure 1. Structure of (−)-englerin A (1).](image)

The dirhodium(II) complex-catalyzed tandem cyclic carbonyl ylide formation/1,3-dipolar cycloaddition reaction of α-diazocarbonyl compounds, which has been extensively studied by Padwa’s group,[10] represents one of the most powerful methods for the rapid assembly of complex oxapolycyclic systems containing embedded di- or tetrahydrofuran rings,[10-12] and an enantioselective version of this sequence employing chiral Rh(II) complexes has also been realized.[13,14] Capitalizing on the carbonyl ylide cycloaddition strategy, Maier et al. reported a concise chiral pool approach toward the oxygen-bridged guaianetype core structure of 1 starting from inexpensive, commercially available (R)-(-)-carveol (Scheme 1).[15] However, contrary to what they expected, cycloaddition of the bicyclic carbonyl ylide 4 generated from Rh₂(OAc)₂-catalyzed dinitrophenyl extrusion of α-diazo-β-ketoester 2 with allyl propiolate (3) occurred exclusively with undesired facial selectivity, wherein the dipolarophile approached the carbonyl ylide 4 syn to the C4 methyl group. In this context, we have reported catalytic enantioselective intermolecular cycloadditions of six-membered carbonyl ylides derived from α-diazo-β-ketoesters with electron-rich acrylate groups in high diastereoselectivity and in excellent yield.

![Scheme 1. Rh(II)-catalyzed carbonyl ylide formation/cycloaddition approach by Maier et al.[15] TES = triethylsilyl.](image)

[a] Dr. T. Hanari, Dr. N. Shimada, Dr. Y. Kuroasaki, Dr. N. Thrimurtulu, Dr. H. Nambu, Dr. M. Anada,* and Prof. Dr. S. Hashimoto* Faculty of Pharmaceutical Sciences Hokkaido University Sapporo 060-0812 (Japan) Fax: (+81)11-706-4981 E-mail: anada@pharm.hokudai.ac.jp, hsmtp@pharm.hokudai.ac.jp Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.
and styrene dipolarophiles using dirhodium(II) tetraakis[N-tetrachlorophthaloyl-(S)-tert-leucinate], [Rh₂(S-TCPTTL)₄] (8),[15] that provide 8-oxabicyclo[3.2.1]octane derivatives with high levels of enantioselectivity (up to 99% ee) and perfect exo-diestereoselectivity for styrenes.[16,17] Intrigued by the oxabicyclo[3.2.1]octane framework carrying the oxygen substituent at C9 on the exo-face found in (−)-englerin A (1), we herein report an alternative approach to 1 highlighting [Rh₂(S-TCPTTL)₄]-catalyzed exo-diestereoselective and enantioselective carbonyl ylide cycloaddition with a vinyl ether dipolarophile as the key step.

Our synthetic strategy for 1 based on the enantioselective carbonyl ylide cycloaddition is outlined retrosynthetically in Scheme 2.[18] Following the precedents,[16] (−)-englerin A (1) would be accessible from tricyclic alcohol 9 bearing all of the stereogenic centers of 1. It was anticipated that 9 would be formed from diketone 10 by intramolecular aldol condensation and stereoselective reduction, which in turn could be elaborated from bicyclic β-stereogenic centers of diketoesters with vinyloxytrimethylsilane or benzyl vinyl ether cycloadditions of carbonyl ylides derived from 2-diazoo-3,6-diketoesters with vinylxytrimethylsilane or benzyl vinyl ether proceeded in a regio- and stereoselective manner to give endo-cycloadducts, wherein the dominant interaction was found to be between the LUMO of the carbonyl ylide and the HOMO of the dipolarophile.[19] Consequently, apart from enantiocontrol, diastereoccontrol in favor of the exo-cycloadduct has become a major challenge in carbonyl ylide cycloaddition with a vinyl ether dipolarophile.

Our synthesis commenced with the preparation of the cyclic carbonyl ylide precursor 12 from succinic anhydride (14) as depicted in Scheme 3. Following the procedure of Schick and Ludwig,[21] Reformatsky reaction of 14 with ethyl 2-bromoisobutyrate in DMF and subsequent decarboxylation provided γ-keto acid 15 in 67% yield. Treatment of 11 with 1,1-carbonyldimidazole (CDI) followed by reaction with the diion derived from tert-butyl hydrogen malonate gave β-ketoester 16[22] in 83% yield, which, upon diazo transfer with methanesulfonyl azide (MsN₃)[23] produced α-diazo-β-ketoester 12 in 96% yield.

Table 1. Enantioselective Carbonyl Ylide Cycloaddition of α-Diazo-β-ketoester 12 with Vinyl Ethers 13 Catalyzed by [Rh₂(S-TCPTTL)₄] (8).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dipolarophile</th>
<th>Cycloadduct</th>
<th>Yield [%]</th>
<th>Ee [%]</th>
<th>Yield [%]</th>
<th>Ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13a Me</td>
<td>11a</td>
<td>53</td>
<td>92</td>
<td>27</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>13b Bn</td>
<td>11b</td>
<td>34</td>
<td>85</td>
<td>17b</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>13c TMS</td>
<td>11c</td>
<td>22</td>
<td>78</td>
<td>17c</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>13d MOM</td>
<td>11d</td>
<td>20</td>
<td>89</td>
<td>17d</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>13e Et</td>
<td>11e</td>
<td>76</td>
<td>95</td>
<td>17e</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>13f nPr</td>
<td>11f</td>
<td>60</td>
<td>92</td>
<td>17f</td>
<td>7</td>
</tr>
</tbody>
</table>

All reactions were carried out as follows: a solution of 12 (107 mg, 0.4 mmol) and dipolarophile 13 (2 equiv) in CF₃C₂H₂ (2 mL) was added over 1 h to a solution of [Rh₂(S-TCPTTL)₄]-2EtOAc (8) (7.9 mg, 0.004 mmol, 1 mol %) in CF₃C₂H₂ (2 mL) at rt. Determined by 1H NMR of the crude product. 

Patterned after our original work,[16a] we initially evaluated the reaction of α-diazo-β-ketoester 12 with methyl vinyl ether (13a) (3 equiv) using 1 mol % of [Rh₂(S-TCPTTL)₄] (8). The reaction in α,α,α-trifluorotoluene at room temperature proceeded smoothly to give a 62.38% mixture of cycloadducts 11a and 17a (Table 1, entry 1). These diastereomers could be separated by column chromatography on silica gel, affording exo-cycloadduct 11a in 53% yield with 92% ee and endo-cycloadduct 17a in 27% yield with 88% ee. Stereochemical assignments of 11a and 17a were obtained from 1H NOE experiments.[24] Encouraged by the observed enantioselectivity, we next examined the reaction of 12 with vinyl ethers 13b-d bearing easily removable protecting groups. Cycloaddition with benzyl- and trimethylsilyl (TMS)-protected vinyl ethers 13b and 13c resulted in a marked drop in exo-selectivity as well as enantioselectivity for exo cycloadducts 11b and 11c (entries 2 and 3), while the use of methoxymethyl (MOM) vinyl ether (13d) provided endo-cycloadduct 17d as a major isomer with 89% ee (exo/endo=23:77, entry 4). Thus, we were pleased to find that the reaction with ethyl vinyl ether (13e) greatly improved the exo-diastereoselectivity (exo/endo=87:13) to give exo-cycloadduct 11e in 76% yield and 95% ee (entry 5). Switching the dipolarophile to propyl vinyl ether (13f) resulted in similar levels of diastereo- and enantioselectivities as those with 13e, but product yield was drastically diminished (entry 6). Clearly, ethyl vinyl ether (13e) proved to be the dipolarophile of choice for this cycloaddition in terms of exo-diastereoselectivity.

![Scheme 2. Retrosynthetic analysis of (−)-englerin A (1).](image-url)

![Scheme 3. Preparation of α-diazo-β-ketoester 12. Reagents and conditions: a) ethyl 2-bromoisobutyrate, Zn, DMF, 65 °C, 2 h; b) hydrochloric acid (18%) 100 °C, 1 h; c) CDI, THF, 1 h; d) tBuO₂CC₂H₂CO₂H, PiMe₂Br, THF, 8 h; e) MnO₂, Et₂N, MeCN, 14 h.](image-url)
and enantioselectivity as well as product yield, though the reason is not clear at present. However, the use of 13e might pose a serious problem of unmasking of the hydroxy group since harsh conditions would be required to cleave the ether bond after cycloaddition. Thus, we were gratified to find that ruthenium tetroxide-catalyzed oxidation of 11e under Sharpless conditions proceeded in a fully chemoselective manner to give the C9 acetate 18 as a sole product in 88% yield, with the oxabicyclic system remaining intact (Scheme 4). From a practical standpoint, it is important to note that the cycloaddition reaction could be conducted on a large scale (16 mmol) with no erosion in yield or selectivity as well as with good recovery of [Rh2(S-TCPPTL)4] (entry 7), though catalyst loading (1 mol%) could not be decreased. Furthermore, a single recrystallization of 11e from ethyl acetate–hexane produced enantiomerically pure material [mp 157.0–159.0 °C, [α]23a]29 –32.5 (c 1.04, CHCl3) in 84% yield (Scheme 5). The preferred absolute configuration of 11e was assigned as (7R,9R,10R) by single-crystal X-ray analysis of carbamate 20 derived from alcohol 19b, which was consistent with that of 1.[27]

Scheme 4. Chemoselective oxidative conversion of the C9 ethyl ether into the C9 acetate.

Scheme 5. Determination of the absolute configuration of 11e. Reagents and conditions: a) recrystallization from EtOAc–hexane; b) NaBH4, EtOH, 0 °C, 1 h; c) (R)-N-methylbenzyl isocyanate, 4-(dimethylamino)pyridine (DMAP), toluene, reflux, 48 h.

With enantiomerically pure exo-cycloadduct 11e in hand, we then focused on elaboration of the tricyclic core structure of (−)-englerin A. Treatment of ketone 11e with sodium bis(trimethylsilyl)amide (NaHMDS) at −78 °C followed by addition of TMSCl and subsequent Ito–Sasegusa oxidation of the resultant silyl enol ether furnished α,β-eneone 21 in 96% yield (Scheme 6). Addition of 2-(2-methyl-1,3-dioxolan-2-yl)ethyl lithium generated from alkyl iodide and iBuLi to enone 21 in THF at −78 °C led to the formation of a diastereomeric mixture of alcohols 23a and 23b in 39% and 37% yields, respectively. Although the oxidation of cyclic tertiary allylic alcohol 23a with pyridinium chlorochromate (PCC) afforded α,β-eneone 24 in good yield, all attempts at oxidative rearrangement of 23b met with failure presumably due to steric hindrance around the C1 position of the epimeric tertiary alcohol. In an effort to improve the stereoselectivity, it was found that the reaction in THF/hexamethylphosphoronic triamide (HMPA) (5:1) at −78 °C provided 23a in 61% yield along with 15% of 23b. In the next step, we anticipated that catalytic hydrogenation of enone 24 should occur from the less hindered exo face to give the desired ketone 25a. Unfortunately, hydrogenation of 24 over Pd/C gave the undesired C1 epimer 25b as a major product. Molecular mechanics calculations revealed that the O-C10-C15=O fragment of 24 adopts an antiperiplanar conformation and that the exo face of the C1–C5 double bond is shielded by the bulky tert-butyl ester. Thus, we reasoned that the stereoselectivity of hydrogenation of this alkenne would be reversed by decreasing the steric hindrance of the ester moiety. Toward this end, allyl alcohol 23a was transformed into α,β-eneone 27 in 73% yield by reduction with sodium bis[2-methoxyethoxy]aluminum hydride (Red-Al)[33] and subsequent tosylation of the primary alcohol followed by oxidative rearrangement.[34] Indeed, hydrogenation of 27 over Pd/C produced the desired ketone 28 as a single diastereomer in virtually quantitative yield. Removal of the ketal protection in 28 was followed by an intramolecular aldo condensation using sodium methoxide in CH2OAc and stereoselective reduction under Luche conditions to afford allylic alcohol 29 as a sole product in 82% yield. Hydroxy group-directed hydrogenation of 29 with Pd/C at room temperature and under 80 atm of H2 provided alcohol 30 as a single diastereomer in 67% yield, along with a small amount (6%) of ketone 31. The stereochemistry of 30 was verified by 1H NOE experiments. The unexpected side product 31 could arise from palladium-catalyzed isomerization of the double bond of 29 on the exo face followed by tautomerization of
A solution of d-diazotoluene (0.6 g, 16.0 mmol) and ethyl vinyl ether (13e) (3.46 g, 48.0 mmol) in a, a′,a′-trifluorotoluene (80 mL) was added dropwise over 1 h to a solution of [Rh2(S-TCPPTTL)I2]2EOAc (B) (302 mg) in dichloromethane (500 mL). A single recrystallization of the recovered B (302 mg) from EIOAc/hexane gave a first crop (222 mg), and the mother liquor was concentrated and the residu was recrystallized from EIOAc/hexane to give a second crop (47 mg). Both crops were of sufficient purity for reuse.

Acknowledgements
This research was supported, in part, by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS) and also by a Grant-in-Aid for Scientific Research on Innovative Areas “Organic Synthesis Based on Reaction Interaction” (No. 2105) from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.H. is grateful to JSPS for a graduate fellowship. We thank S. Oka, M. Kiuchi and H. Hisote from the Center for Instrumental Analysis at Hokkaido University for mass measurements and elemental analysis.

Keywords: (−)-englerin A • enantioselective total synthesis • carboxyl ylide • 1,3-dipolar cycloaddition • diiodonium (II) complexes


