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# Total Synthesis of (±)-Cafestol: A Late-Stage Construction of the Furan Ring Inspired by a Biosynthesis Strategy

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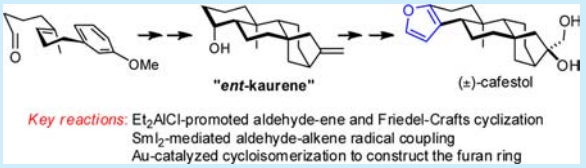
Supporting Information

**ABSTRACT:** An efficient bioinspired approach to the total synthesis of (±)-cafestol features a late-stage installation of the furan ring with a mild Au-catalyzed cycloisomerization. The $Et_2AlCl$-promoted aldehyde−ene cyclization and subsequent Friedel−Crafts reaction deliver a requisite tricyclic system in gram scale with high stereo- and regioselectivity. Moreover, a highly stereoselective $SmI_2$-mediated aldehyde−alkene radical cyclization furnishes the key bicyclo[3.2.1]octane skeleton to offer an advanced intermediate for the synthesis of other oxygenated *ent*-kaurene diterpenoids.




*ent*-Kaurene is an important member of diterpenoids, and the diverse and intriguing structural features have been extensively studied from both the enzymology and chemical synthesis prospects.[1] Cafestol (**2**) and kahweol (**3**), two *ent*-kaurene (**1**) derived diterpenoids bearing a unique furan ring, were isolated from unfiltered coffee drinks (Figure 1).[2] These diterpenoids

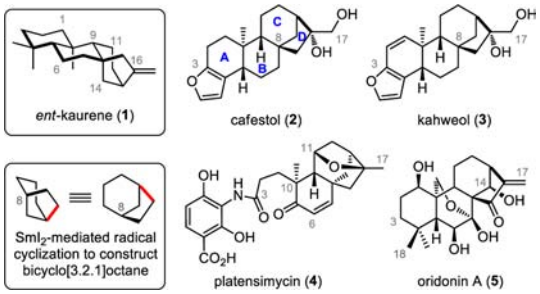
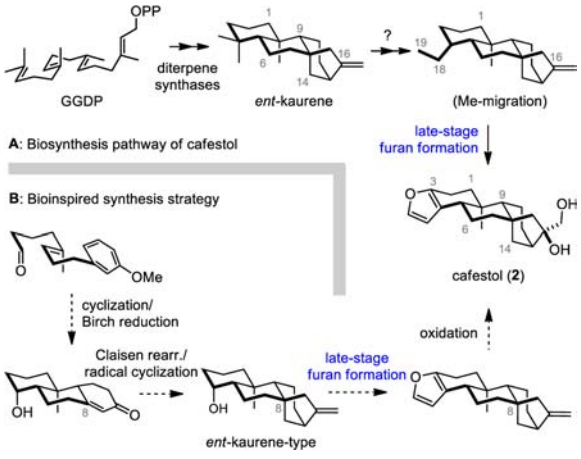



**Figure 1.** Representative *ent*-kaurene diterpenoids.

have exhibited interesting bioactivities, such as anti-inflammation, cholesterol elevation, and a neuroprotective effect,[3] and were recently discovered to induce apoptosis through regulation of specificity protein 1 (Sp1) expression in human malignant pleural mesothelioma (HMPM)[4] which is considered a highly aggressive cancer with a poor prognosis. Biogenetic derivatization of *ent*-kaurene (**1**) to cafestol (**2**) may consist of a methyl migration from C(18) or C(19) and subsequent furan formation in conjunction with the A-ring (Scheme 1A). The exhausted degradation of three carbons at C(4), C(18), and C(19) was found in a recently isolated potent antibiotic platensimycin (**4**).[5] Moreover, ample hydroxyl groups in the *ent*-kaurene skeleton play a vital role in potent anticancer agent oridonin A (**5**).[6] The common feature of a bicyclo[3.2.1]octane in the complex structures above emphasizes that a general strategy shall embrace flexibility in installing hydroxyl groups at C(11) and C(14), respectively.[7] We have been engaged in devising an efficient

**Scheme 1. Inspiration of Biosynthesis Strategy**




approach to construct the requisite pentacyclic system. As a proof of concept, the total synthesis of cafestol is presented here.

With continuing interest in the biomimetic synthesis of natural products,[8] we envisaged the efficient construction of the pentacyclic structure may generate an array of downstream compounds in parallel with the pipeline of cafestol biosynthesis.[9] An essential late-stage construction of furan, whose sensitivity was revealed in Corey's landmark synthesis,[10] is outlined (Scheme 1B). A $SmI_2$-mediated radical cyclization of an aldehyde and alkene is designed as the linchpin for the construction of bicyclo[3.2.1]octane, and a Claisen rearrangement will furnish the quaternary carbon center of C(8). To achieve this goal, the aldehyde−ene initiated cyclization programmed for the tricyclic system should be highly stereo- and regioselective. To the best of our knowledge, the polyene-type cyclization begun from

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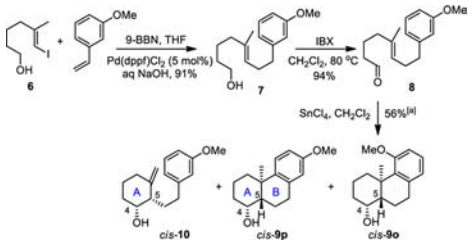
aldehyde is not well-established and remains largely unexplored.[8c]

A chain elongation of 3-methoxystyrene was realized through a Suzuki coupling with vinyliodide **6**, which was readily prepared with Negishi's protocol (Scheme 2).[11] Initial Swern oxidation of

**Scheme 2. Cyclization of (*E*)-Enal 8**



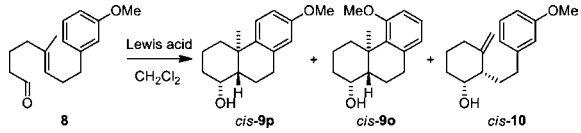

[a]Yield includes *cis*-**9p** and *cis*-**9o** (*ds* 3/1 for the relative configuration of C(4) and C(5) in **9**; regioselectivity, *cis*-**9p**/*cis*-**9o** = 2.4/1).

corresponding alcohol **7** gave (*E*)-enal **8** in 45% yield along with a considerable amount of tricyclic products (stereochemistry undefined, ~20% combined yield). Further experiments revealed a trace amount of acid, generated under the oxidation conditions, was responsible for the contaminated cyclization. IBX was finally identified as the optimal oxidation reagent, affording enal **8** in excellent yield (94%, 20-g scale). Following Yamamoto's conditions,[12] $SnCl_4$ promoted the cyclization to give cyclized compounds *cis*-**9p** and *cis*-**9o** in a combined 56% yield. However, both stereoselectivity (*ds* 3/1) and regioselectivity (para-/ortho-, 2.4/1) were not appealing (Scheme 2). The preference of an axial hydroxyl group at C(4) (*ds* 3/1) was confirmed by 2D NOE analyses of *cis*-**9o** and *cis*-**9p**.[13] During the cyclization reaction, the major intermediate *cis*-**10** was also identified. This product, which lacks the conjunct B-ring, is probably derived from the Lewis acid mediated aldehyde–ene reaction or incomplete cationic cyclization.[14]

As denoted in Snider and Brown's model, the stereoselectivity of aldehyde–ene cyclization shows a preference for a chairlike conformation if an aluminum complex was chosen.[14] The low selectivity associated in the cyclization of enal **8** may be attributed to complex reaction pathways under the promotion of $SnCl_4$. Moreover, application of an ene cyclization in a system such as **8** is not yet explored in total synthesis.[12a,15] Therefore, we decided to investigate the aldehyde–ene reaction instead of a direct cationic cyclization which may result in several cyclized products. Several Lewis acids were thus examined. Moderate regioselectivities and isolated yields of *cis*-**9p** were obtained when $TiCl_4$, $BF_3{\cdot}Et_2O$, and $EtAlCl_2$ were used (entries 1 to 4 in Table 1). Milder Lewis acids such as $Me_2AlCl$ and $Et_2AlCl$ yielded good *cis*-selectivity and isolated yields for the carbonyl–ene cyclization (entries 5 and 6). When $Me_3Al$ was chosen, exceptional regioselectivity (*p*/*o*: >20/1) and *trans*-selectivity (*c*/*t*: <1/20) were achieved, albeit in a lower isolated yield due to the nucleophilic addition of aldehyde (*trans*-**9p**, 46%, entry 7).[16] For a synthetically useful scale (>2 g), the optimized conditions still maintain high stereo- and regioselectivity to deliver *cis*-**9p** in 75% yield (entry 8 vs 6).[17] Since the *meta*-methoxyphenyl termination in cationic cyclization has been challenging in literature precedents,[18−20] the excellent regioselectivity achieved here is particularly rewarding.

It was further discovered that the stereoselectivity can be switched where *trans*-**9p**[13] was isolated in 73% yield when the reaction temperature was quickly raised to rt (entry 9, Table 1). A

**Table 1. Optimization of Aldehyde–Ene Initiated Cyclization[a]**

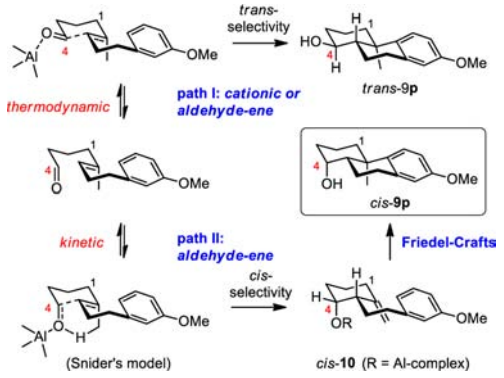



| | | *cis*-**10** | **9** | | |
|---|---|---|---|---|---|
| entry | reaction conditions | yield (%) | *c*/*t*[b] | p/o[b] | yield (%)[c] |
| 1 | $SnCl_4$ (1.5), −78 °C, 9 h | – | 3/1 | 2.4/1 | 56 |
| 2 | $TiCl_4$ (1.5), −78 °C, 9 h | – | 3.7/1 | 2.1/1 | 47 |
| 3 | $BF_3{\cdot}Et_2O$ (1.5), −78 °C, 9 h | – | 5/1 | 4.2/1 | 65 |
| 4 | $EtAlCl_2$ (1.5), −78 °C, 9 h | – | 4.5/1 | 3.1/1 | 55 |
| 5 | $Me_2AlCl$ (1.5), −78 °C, 9 h | 10 | 13/1 | 11.8/1 | 80 |
| 6 | $Et_2AlCl$ (1.5), −78 °C, 9 h | 10 | 13/1 | 12.8/1 | 81 |
| 7[d] | $Me_3Al$ (3.5), −78 °C, 9 h | – | <1/20 | >20/1 | 46[e] |
| 8[f] | $Et_2AlCl$ (1.5), −78 °C, 14 h | <5 | 12.3/1 | 12.5/1 | 75 |
| 9[g] | $Et_2AlCl$ (0.9), 0 °C, 30 min; rt, 8 h | – | <1/20 | 8/1 | 73[e] |

[a]Reaction conditions: aldehyde **8** (125 mg, 0.5 mmol, 0.2 M), $CH_2Cl_2$ (2.5 mL), Lewis acid (1.0 M in $CH_2Cl_2$ or hexanes, 0.9–3.5 equiv), −78 °C to rt. [b]Stereoselectivity (*c*/*t*: *cis*/*trans*) and regioselectivity (p/o: para-/ortho-) were determined by $^1H$ NMR (400 MHz, $CDCl_3$). [c]Combined yields of *cis*-**9p** and *cis*-**9o** for entries 1–6; isolated yield of *cis*-**9p** for entry 8. [d]A severe nucleophilic addition of aldehyde with the Me group from $Me_3Al$ was found. [e]*Trans*-**9p** was isolated ($C_4$–OH is equatorial) for entries 7 and 9. [f]2.4-g scale. [g]13-g scale; $Et_2AlCl$ (0.9 M in toluene) was used.

thermodynamically favorable trans-isomer may be derived from an ene cyclization through a boatlike conformation or a cationic process (Scheme 3).[14b] The diastereoselectivity switch beneficially provides impetus for initiating strategic C–H activation to access different synthetic targets.[21]

**Scheme 3. Stereochemistry Switch in Cyclization**




With a sufficient amount of compound *cis*-**9p** in hand, we turned our attention to the construction of the bicyclo[3.2.1]-octane architecture (Scheme 4). The Birch reduction using lithium, *tert*-butyl alcohol, and liquid ammonia in THF with an acidic workup afforded enone **11** in 78% yield. Luche reduction yielded allylic alcohol **12** in a 9:1 ratio favoring the *β*-configuration. The subsequent Eschenmoser–Claisen rearrangement proceeded smoothly establishing the quaternary carbon center of C(8) in **13** (72% yield).[22] Neutral conditions in this step were crucial for diminishing a dehydration side reaction, observed with reaction conditions in other variants of the Claisen rearrangement which require acid catalysts. Subsequently, the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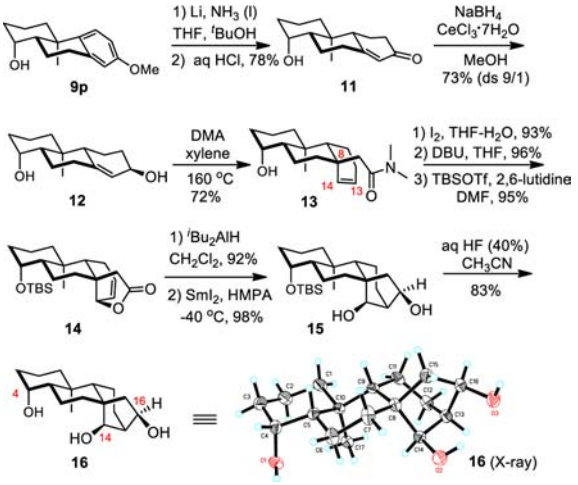
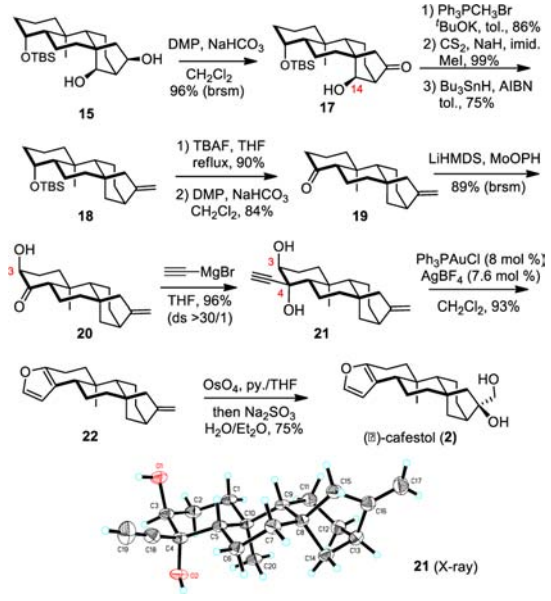
**Scheme 4. Synthesis of Core Structure**




iodine-mediated esterification and base-promoted elimination provided a bonus in double bond migration from C(13)−C(14) to C(12)−C(13).[23] DIBALH reduction of the lactone to the lactol, followed by $SmI_2$-mediated radical cyclization,[24] exclusively furnished diol **15** in 98% yield. The stereochemistry of **15** was unambiguously established by X-ray analysis of **16** after removal of the TBS protecting group.[25] The excellent stereochemistry control in the radical cyclization may rely on the participation of the $\beta$-OH at C(14) through the coordination with Sm(III).[26]

Oxidative differentiation of two secondary alcohols at C(14) and C(16) in **15** was realized due to differences in steric hindrance. Wittig olefination and subsequent Barton−McCombie radical deoxygenation[27] furnished the requisite bicyclo[3.2.1]octane **18** in excellent yield (Scheme 5). To complete the synthesis, oxidative manipulation of the A-ring in **18** required hydroxylation at C(3) and the formation of the fused furan. Thus, after removal of the TBS protecting group and subsequent oxidation, the corresponding ketone **19** was then treated with LiHMDS and hydroxylated with Vedejs' reagent

**Scheme 5. Completion of the Synthesis of (±)-Cafestol**




$(MoO_5(py)(HMPA))$[28] to give **20** as a single diastereomer in 89% yield (b.r.s.m., 77% conv). After reaction with ethynylmagnesium bromide in THF, the major stereoisomer of corresponding adduct **21** was isolated and its structure was unambiguously established by X-ray analysis.[25] The following furan formation was realized with a protocol developed by Akai and co-workers.[29] However, the original gold-catalyst system afforded furan **22** with contamination of the double bond migrated product.[30] We envisioned the existence of a silver salt may elicit the exoalkene isomerization.[31] Therefore, after the anion metathesis, the silver salt was filtered off through a nylon membrane and the resulting "Au catalyst" was directly used for the subsequent cycloisomerization. The requisite furan was formed in 93% yield without any detectable isomerized product. Dihydroxylation with stoichiometric osmium tetroxide followed by cleavage of the bisosmate with sodium sulfite completed the total synthesis of (±)-cafestol (**2**) whose spectra were identical with the reported data.[10a,32]

The synthesis described here illustrates a bioinspired approach to (±)-cafestol in 20 steps from vinyliodide **6**. Two aldehyde−alkene cyclizations are particularly noteworthy. Namely, the aldehyde−ene cyclization coupled with a Friedel−Crafts reaction furnished the requisite tricyclic system in high stereo- and regioselectivity. The following $SmI_2$-promoted lactol−alkene coupling established the key bicyclo[3.2.1]octane skeleton to offer an advanced intermediate for the synthesis of other oxygenated *ent*-kaurene diterpenoids, especially those bearing a C(14)−$\beta$-OH group (such as in **5**). Furthermore, it features a late-stage Au-catalyzed furan formation leading to a mild and efficient protocol to introduce the sensitive furan moiety in complex targets. Future manipulation of the A-ring would provide versatile analogues for enriching the structure−activity relationship of cafestol. Development of enantioselective synthesis of the potent lead and further exploration of the bioinspired approach leading to diverse *ent*-kaurene diterpenoids are currently underway in this laboratory.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental details, spectra of synthetic intermediates, and X-ray diffractions of compounds **16** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION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### Author Contributions

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### Notes

The authors declare no competing financial interest.

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(25) CCDC 969986 (**16**) and CCDC 973471 (**21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk.

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(32) The chemical shift for the angular methyl group {C(20)} was mistakenly reported as $\delta$ 33.3 ppm in the original document; however, our data is much more shielded ($\delta$ 13.3 ppm). For a comparison of the carbon-13 NMR, see the Supporting Information for details.