



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

Lili Zhu,[†] Jisheng Luo,[†] and Ran Hong*

CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: An efficient bioinspired approach to the total synthesis of (\pm) -cafestol features a late-stage installation of the furan ring with a mild Au-catalyzed cycloisomerization. The Et₂AlCl-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 SmI₂-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





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 SmI₂-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 tricylic system should be highly stereo- and regioselective. To the best of our knowledge, the polyene-type cyclization begun from

Received: February 26, 2014 Published: April 1, 2014 aldehyde is not well-established and remains largely unexplored. $^{\mathrm{8c}}$

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*-**9** \mathbf{p} and *cis*-**9** \mathbf{o} (*ds* 3/1 for the relative configuration of C(4) and C(5) in **9**; regioselectivity, *cis*-**9** \mathbf{p} /*cis*-**9** \mathbf{o} = 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 SnCl₄ 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-90 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 SnCl₄. 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 TiCl₄, BF₃. Et₂O, and EtAlCl₂ were used (entries 1 to 4 in Table 1). Milder Lewis acids such as Me2AlCl and Et2AlCl yielded good cisselectivity and isolated yields for the carbonyl-ene cyclization (entries 5 and 6). When Me₃Al 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

 7^d

8^f

og

Me₃Al (3.5), -78 °C, 9 h

Et₂AlCl (1.5), -78 °C, 14 h

Et₂AlCl (0.9), 0 °C, 30 min;



<5

<1/20

12.3/1

<1/20

>20/1

12.5/1

8/1

46^e

75

73^e

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



With a sufficient amount of compound *cis*-9**p** 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

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 SmI₂-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 β -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 deoxygenation²⁷ 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





 $(MoO_5(py)(HMPA))^{28}$ 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 (\pm) -cafestol (2) whose spectra were identical with the reported data.^{10a,32}

The synthesis described here illustrates a bioinspired approach to (\pm) -cafestol in 20 steps from vinyliodide 6. Two aldehydealkene 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 SmI2-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

Corresponding Author

*E-mail: rhong@sioc.ac.cn.

Author Contributions

[†]These authors contributed equally.

Notes

The authors declare no competing financial interest.

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