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Formal synthesis of (−)-oleocanthal by means of a SmI_2-promoted intramolecular coupling of bromoalkyne with α,β-unsaturated ester

Kazunori Takahashi, Hiroshi Morita, Toshio Honda *

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

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ABSTRACT

A novel approach to the synthesis of (−)-oleocanthal starting from D-ribose, in which a SmI_2-promoted intramolecular coupling of bromoalkyne with α,β-unsaturated ester is a key step, has been developed.

(−)-Oleocanthal **1**, isolated from extra virgin olive oil, is a naturally occurring minor phenolic secoiridoid.[1] Olive oil has being consumed for many centuries in Mediterranean countries, and it is known to reduce the risk of cardiovascular system diseases due to both its high content of monounsaturated fatty acids and its high content of anti-oxidative substances (Fig. 1).

(−)-Oleocanthal **1** shows both a potent NSAID (non-steroidal anti-inflammatory drug) activity by inhibiting COX-1 and COX-2, similar to ibuprofen,[2] and an anti-oxidant activity. It has also been reported that **1** prevents tau fibrillization of Aβ amyloid to provide novel therapies for neurodegenerative tauopathies such as Alzheimer's disease.[3] Therefore, oleocanthal and its derivatives are expected to be important leads and scaffolds for the discovery and development of drugs to treat inflammatory osteoarthritis and Alzheimer's disease. Oleocanthal **1** has received much attention due to its attractive biological activities and also its unique structural features, and several synthetic methods have been developed to date.[4]

Recently, we have established a samarium diiodide-promoted intramolecular coupling reaction of bromoalkynes with α,β-unsaturated esters that provides functionalized five-membered carbocycles and heterocycles with high diastereoselectivities in excellent yields[5] (Scheme 1).

In our continuing work on the synthesis of biologically active natural products by means of samarium diiodide, we were interested in the synthesis of oleocanthal **1** by application of the above methodology, and we decided to prepare Smith's intermediate (−)-**2** for synthesis of the target compound, because a coupling product having a functionalized cyclopentane ring system with an *exo*-bromomethylene unit seemed to be a structural feature closely related to Smith's intermediate (−)-**2**.[4a,b]

We first attempted the synthesis of (+)-oleocanthal ***ent*-1**, an antipodal form of the natural product, to investigate whether the desired coupling could proceed smoothly or not, because we thought that a precursor for the key coupling reaction could easily be prepared from a readily available chiral source, 2-deoxy-D-ribose.

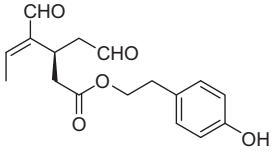
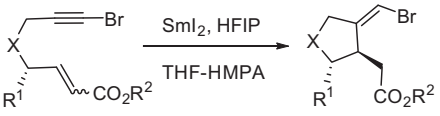


Figure 1. Structure of (−)-oleocanthal.



X = CH_2, O, NTs, R^1, R^2 = alkyl

Scheme 1. SmI_2-promoted intramolecular coupling reaction.

* Corresponding author. Tel./fax: +81 3 5498 5791.
E-mail address: honda@hoshi.ac.jp (T. Honda).

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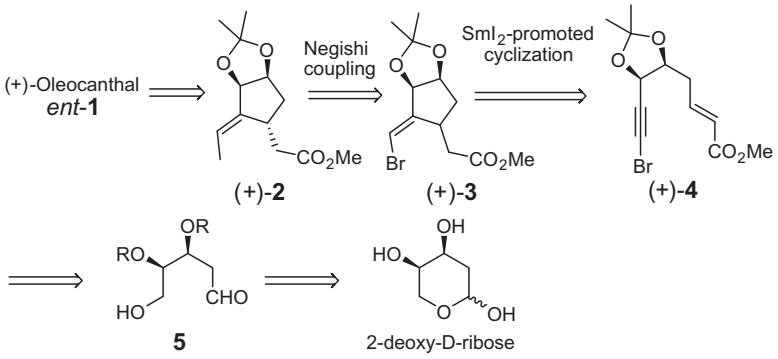


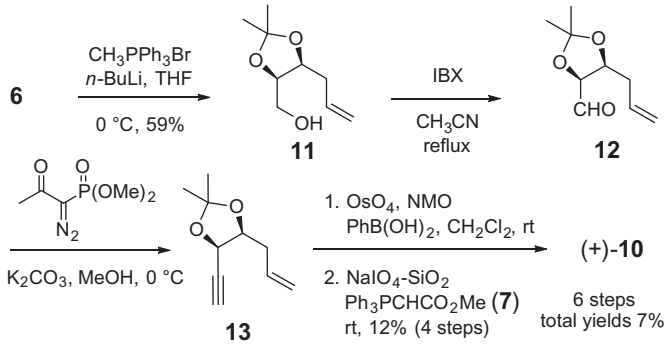
Scheme 2. Retrosynthetic route to (+)-oleocanthal ***ent*-1**.

Our basic strategy for the synthesis of (+)-oleocanthal ***ent*-1** is outlined in Scheme 2. The *exo*-ethylidene unit existing in Smith's intermediate will be derived from the corresponding *exo*-bromoalkene (+)-**3** by palladium-catalyzed chemical modification with methylzinc chloride. The functionalized cyclopentane derivative with a bromoalkene unit will also be constructed by a samarium diiodide-promoted intramolecular coupling reaction of bromoalkynes (+)-**4** with α,β-unsaturated esters, obtained from 2-deoxy-D-ribose.

Thus, 2-deoxy-D-ribose was converted into acetonide **6**, which on treatment with Wittig reagent **7** furnished exclusively the *E*-ester **8** in 74% yield. Swern oxidation of the hydroxy group of **8** afforded the known aldehyde **9**.[7] The product was then reacted with the Ohira–Bestmann reagent[6] in the presence of K_2CO_3 to afford alkyne derivative (+)-**10** in trace, presumably due to its instability under basic conditions (Scheme 3).

Although this approach is still being explored, an alternative route to (+)-**1** in which introduction of the alkynl group is conducted prior to construction of the α,β-unsaturated ester group, was developed (Scheme 4). Wittig reaction of acetonide **6** with unstable ylide in THF provided the alkene **11**[8] in 59% yield. The alkene **11** was oxidized with *o*-iodoxybenzoic acid (IBX)[9] to the corresponding aldehyde **12**, which was then treated with Ohira–Bestmann reagent to afford alkyne derivative **13**.

The resulting alkyne **13** was treated with OsO_4 in the presence of phenylboronic acid,[10] followed by $NaIO_4$ on silica gel[11a] in the presence of stable ylide **7**,[11b] to afford an eneyne intermediate (+)-**10** in 12% over four steps. Attempted transformation of alcohol **11** into the eneyne derivative (+)-**10** gave unsatisfactory results (six steps, total yield of 7%), prompting us to find another route. Although alkyne **10** was obtained only in a small amount, a key coupling was attempted as follows.

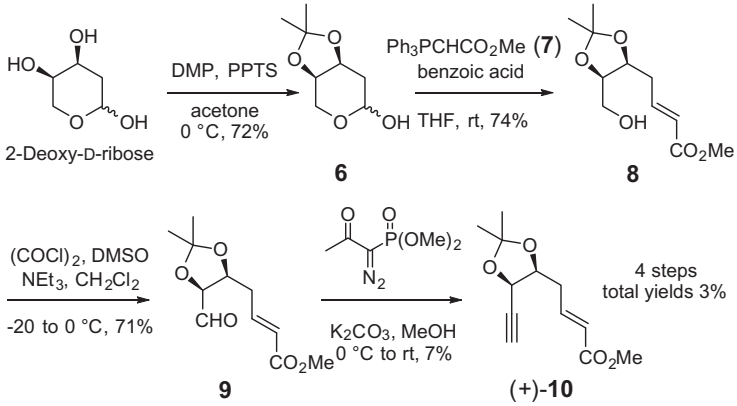


Scheme 4. Alternative synthesis of (+)-**10**.

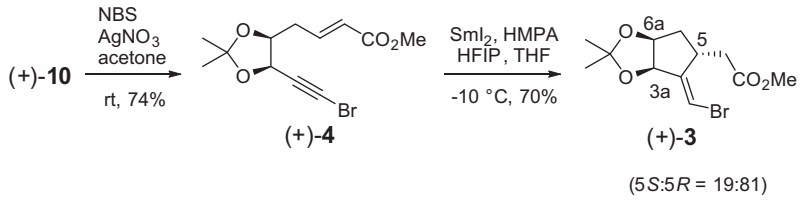
Alkyne **10** was brominated with NBS and $AgNO_3$ in acetone to give bromoalkyne **4**, which on treatment with samarium diiodide in THF-HMPA in the presence of hexafluoroisopropanol (HFIP) at −10 °C for 1 h afforded the desired cyclopentane derivative **3** as a mixture of diastereoisomers in 70% yield (Scheme 5).

Since the key intramolecular coupling of (+)-**4** took place successfully under the reaction conditions mentioned above, we decided to start the synthesis of (−)-oleocanthal **1** along this strategy. The novel synthetic route for **1** is illustrated in Scheme 6.

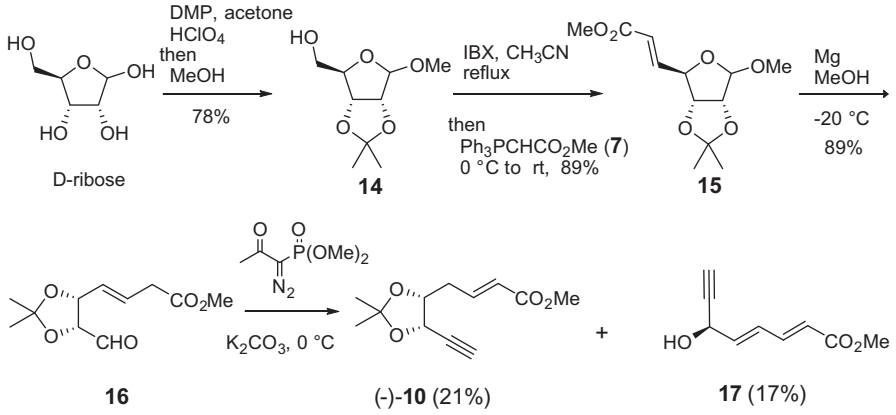
D-Ribose was converted into acetonide **14** in 78% yield according to the known procedure.[12] Construction of the α,β-unsaturated ester was accomplished by successive treatments of **14** with (i) IBX and (ii) Wittig reaction of the resulting aldehyde, to give an unsaturated ester derivative **15** in 89% yield over two steps. The ester **15**



Scheme 3. Preparation of alkyne derivative (+)-**10**.



Scheme 5. Attempted coupling reaction of (+)-**10**.

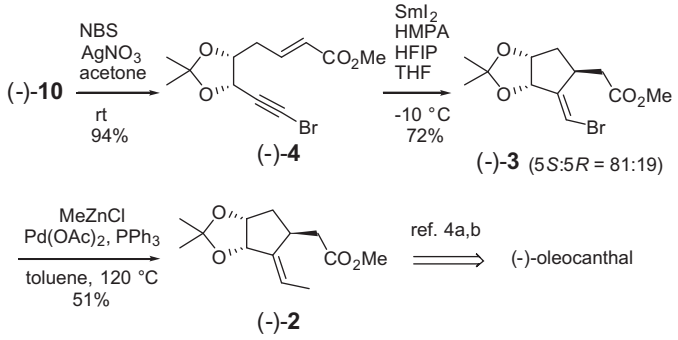


Scheme 6. Preparation of alkyne derivative (−)-**10**.

was treated with Mg powder in MeOH at −20 °C[13a] to give a β, γ-unsaturated ester **16**, reported by Gallos,[13b] in 89% yield. Treatment of **16** with Ohira–Bestmann reagent resulted in simultaneous formation of an alkyne group and double bond isomerization, providing the desired alkyne intermediate (−)-**10** in 21% yield. Again, the low yield in the formation of **10** might be due to its instability under basic conditions, since the elimination product **17** was obtained as the major side-product in 17% yield together with a number of structurally unidentified decomposed products.

Bromination of the resulting alkyne (−)-**10** with NBS and $AgNO_3$ in acetone afforded bromoalkyne (−)-**4**[14] in 94% yield. Treatment of bromoalkyne (−)-**4** with samarium diiodide in THF-HMPA in the presence of HFIP at −10 °C for 1 h provided vinyl bromide (−)-**3**[15] with an (*E*)-configuration, in a ratio of *trans*:*cis* = 81:19, in 72% yield. The stereochemistry of the product was unambiguously determined on the basis of 2D NMR spectroscopy and NOE. The stereoselectivity exhibited in the formation of *trans*-**3** as the major product can be rationalized by assuming that this cyclization would proceed via the more sterically and energetically favorable (**A**) rather than (**B**) as depicted in Figure 2.

Finally, palladium-catalyzed coupling reaction of vinyl bromide (−)-**3** with methylzinc chloride in toluene gave the known intermediate (−)-**2** in 51% yield (Scheme 7). The observed low yield probably arose from a decomposition of the acetonide group at relatively high temperature employed for this conversion.



Scheme 7. Formal synthesis of (−)-oleocanthal **1**.

The specific optical rotation of the bicyclo derivative (−)-**2** {$[\alpha]_D^{18}$ −123.8 (*c* 0.45, $CHCl_3$)} was identical to that reported $[\alpha]_D^{18}$ −128.4 (*c* 0.75, $CHCl_3$)] in the literature.[4a,b]

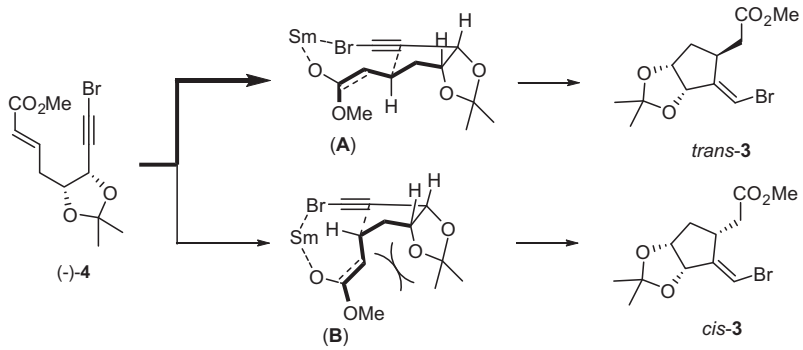


Figure 2. Plausible mechanism for the coupling of (−)-**4**.

Thus, a formal synthesis of (−)-oleocanthal **1** was achieved at this stage; however, some improvement is required to optimize the reaction sequences.

In conclusion, we were able to establish a formal synthesis of (−)-oleocanthal **1** by employing a SmI_2-promoted coupling reaction as the key step, in which stereoselective construction of the newly generated stereogenic center and introduction of *exo*-olefin were achieved in one step. We believe that this synthetic strategy has great potential for the synthesis of a wide range of natural products bearing such a cyclic system.

Acknowledgments

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14. *Selected data for compound (−)-***4**: $[\alpha]_D^{18}$ − 49.7 (*c* 0.83, $CHCl_3$); IR (neat) 2989, 1725, 1222 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.96 (1H, dt, *J* = 15.7, 7.1 Hz), 5.97 (1H, dt, *J* = 15.7, 1.5 Hz), 4.80 (1H, d, *J* = 5.5 Hz), 4.19 (1H, dt, *J* = 7.1, 5.5 Hz), 3.74 (3H, s), 2.73–2.56 (2H, m), 1.53 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 143.7, 123.4, 110.1, 76.1, 75.8, 69.5, 51.3, 48.2, 33.8, 27.5, 25.1; HRMS (CI) *m*/*z* 303 (M+H) Calcd for $C_{12}H_{16}O_4Br$ 303.0231. Found 303.0242.
15. *Selected data for compound (−)-***3**: $[\alpha]_D^{19}$ −138.9 (*c* 0.59, $CHCl_3$); IR (neat) 2987, 1738, 1218 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.35 (1H, dd, *J* = 2.3, 1.8 Hz), 4.91 (1H, dd, *J* = 5.3, 1.8 Hz), 4.68 (1H, ddd, *J* = 5.3, 5.3, 2.0 Hz), 3.68 (3H, s), 3.34–3.32 (1H, m), 2.87 (1H, dd, *J* = 16.6, 4.0 Hz), 2.62 (1H, dd, *J* = 16.6, 8.5 Hz), 2.29 (1H, ddd, *J* = 9.0, 4.6, 2.0 Hz), 1.86 (1H, ddd, *J* = 14.6, 6.8, 5.5 Hz), 1.43 (3H, s), 1.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 149.8, 111.7, 105.1, 82.7, 80.2, 51.5, 38.3, 36.7, 34.8, 27.6, 25.8; HRMS (CI) *m*/*z* 291 (M+H-CH_3) Calcd for $C_{11}H_{14}O_4{}^{81}Br$ 291.0055. Found 291.0025.