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ARTICLE *in* CHEMISTRY - AN ASIAN JOURNAL · JUNE 2014

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Enantiospecific Synthesis and Cytotoxicity Evaluation of Ligudentatol: A Programmed Aromatization Approach to the 2,3,4-Trisubstituted Phenolic Motif via Visible-Light-Mediated Group Transfer Radical Cyclization

Gamal A. I. Moustafa, Hiroshi Suizu, Hiroshi Aoyama, Masayoshi Arai, Shuji Akai, and Takehiko Yoshimitsu*[a]

Abstract: A facile enantiospecific approach to (+)-ligudentatol (**1**) and (−)-ligudentatol (*ent*-**1**) is reported. The approach features the construction of a trisubstituted phenolic motif fused to a chiral aliphatic ring by a sequence of visible-light-mediated radical seleno transfer cyclization, bromination, concomitant selenoxide elimination–dehydrobromination, and demethoxycarbonylation, namely, a programmed aromatization. Biological evaluation of the enantiomers of ligudentatol obtained by the present route revealed for the first time their cytotoxicity towards various cancer cell lines.

Natural phenols are a rich source of bioactive materials that exhibit antioxidant, cytotoxic, and antibacterial activities. (+)-Ligudentatol (**1**), a unique trisubstituted phenolic norsesquiterpene isolated from the rhizomes of the perennial herb *Ligularia dentata* Hara in 1990 by Naya and coworkers, is a member of 14-noreudesmanes (Figure 1).[1] In 1998, Jia and Gao reported that (+)-liguhodgsonal (**2**), a closely related phenol isolated from the roots of *Ligularia dentata* Cass., exhibited strong antiproliferative activities against human hepatoma (H-7402), human myelogenous leukemia (K562), and mouse melanin carcinoma (B16) cell lines.[2] In our unrelenting effort to develop natural products-based medicinal resources,[3,4] ligudentatol (**1**) caught our attention and prompted us to assess its potential biological activity. Herein, we report a facile approach to the enantiomers of ligudentatol, which features visible-light-mediated seleno transfer radical cyclization, followed by aromatization. Furthermore, the cytotoxicity of synthetic (+)-ligudentatol (**1**) and (−)-ligudentatol (*ent*-**1**) toward various cancer cell lines is demonstrated for the first time, paving the way for the development of new antiproliferative agents of natural origin.

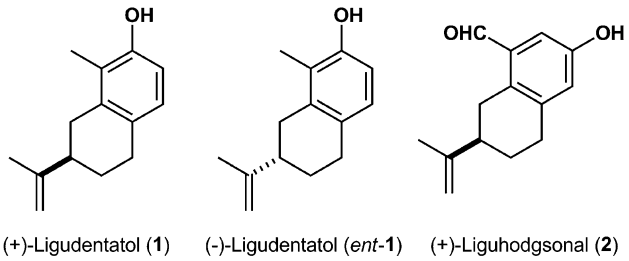
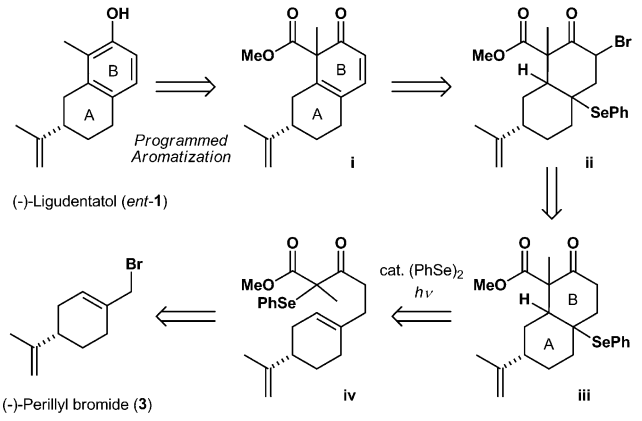


Figure 1. Ligudentatol (**1**) and liguhodgsonal (**2**).

An enantioselective synthesis of natural (+)-ligudentatol (**1**) was previously reported by Haddad and Salman, who devised a [2+2] photochemical access to the phenolic motif.[5] Our synthetic route to ligudentatol features the construction of a phenolic core by facile aromatization of highly functionalized decalin system **iii** that is accessible by seleno transfer radical cyclization of **iv** (Scheme 1).[6,7] Intermediate



Scheme 1. Retrosynthesis of (−)-ligudentatol (*ent*-**1**).

iv, the precursor of decalin scaffold **iii**, is readily obtainable from perillyl bromide (**3**) in an optically pure form. It has been well documented in the literature that, unlike reductive radical cyclizations that are commonly terminated by hydrogen abstractions, atom or group transfer approaches allow the cyclized material to bear functionalities suitable

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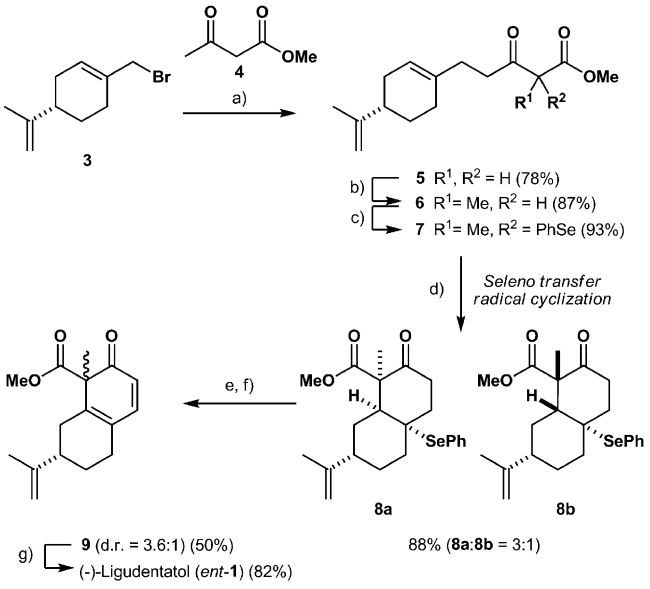
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/asia.201400110.

for further chemical transformations. This is the case for our approach to ligudentatol in which a phenylseleno functionality is transferred to the ring system and a bromide is installed thereafter to set the stage for dienone formation. Dienone **i**, obtainable by simple elimination reactions of the functionalities is converted into phenol **1** by thermodynamically favorable aromatization.

(−)-Perillyl bromide (**3**),[8] which was obtained from (*S*)-perillaldehyde in two steps, was reacted with a dienolate generated from methyl acetoacetate (**4**) using two equivalents of LDA at −78 °C to furnish ester **5** in 78 % yield (Scheme 2). Ester **5** was then treated with methyl iodide in the presence of K_2CO_3 in acetone at 60 °C to afford compound **6** in 87 % yield. Selenylated compound **7** (d.r. = 1:1) was prepared by installing a phenylseleno functionality into the α-position of β-keto ester **6** by treatment with NaH followed by phenylselenyl chloride at −40 °C in THF.



Scheme 2. Total synthesis of (−)-ligudentatol (*ent*-**1**). Reagents and conditions: a) LDA (2 equiv), THF, −78 °C; b) K_2CO_3, MeI, acetone, 60 °C; c) PhSeCl, NaH, THF, −40 °C; d) cat. $(PhSe)_2$, *hν* (visible light), CH_2Cl_2, 0 to 5 °C; e) LDA, NBS, THF, −78 °C; f) H_2O_2, THF, pyridine, rt, then Me_2S, DBU, rt, 50 % over 2 steps; g) μW, NaCl, aq. DMSO, 200 °C

With this selenide **7**, the key group transfer radical cyclization was examined. Pioneering studies on the addition of carbon–selenium (C–SePh) bonds to carbon–carbon multiple bonds were recorded by Byers,[9] Curran,[10] Back,[11] and Renaud,[12] who disclosed the utility of the seleno transfer processes under radical conditions.[13] Yang and co-workers also reported highly stereoselective seleno transfer cyclizations of alkenylated α-phenylseleno-β-keto and α-phenylseleno-β-hydroxyesters.[14]

We opted to adopt visible-light irradiation to promote the seleno transfer processes. Substrate **7** was irradiated by a tungsten lamp (150 W) in the presence of 0.2 equivalent of diphenyldiselenide in CH_2Cl_2 at 0 to 5 °C to produce cyclized products **8a** and **8b** in a diastereomeric ratio of 3:1 (the reaction time necessary for the consumption of **7** was 3 h; Table 1, entry 2). Diphenyldiselenide was essential for efficient transformation: its omission led to poor conversion (~30 % yield after 3 h; Table 1, entry 1). It should be noted that at higher temperature (i.e., in refluxing CH_2Cl_2), the reaction was accelerated to provide the cyclized compounds in 90 % yield, albeit with lower diastereoselectivity (**8a**:**8b** = 2:1; Table 1, entry 3). Although the stereochemistry of major product **8a** could not be elucidated at this stage, minor cyclized material **8b** fortunately gave a crystalline material suitable for X-ray analysis. The analysis showed that compound **8b** has a *trans*-decalin architecture with a β-configurational methyl substituent (Figure 2).[15] On the other hand, after several trials to determine the stereochemistry of major product **8a**, we were delighted to find that, by visible-light irradiation in the presence of diphenyldiselenide in refluxing dichloroethane, compound **8a** (a diastereomerically enriched material with a ratio **8a**:**8b** = 7.5:1) underwent epimerization at the selenylated carbon to afford compound **10** (Figure 3). The stereochemistry of the ring juncture of compound **10** was unambiguously confirmed again by X-ray crystallography and to our surprise, it was *trans*.[16] The epimerization likely took place via radical scission of the carbon–selenium (C–SePh) bond by S_H2 reaction with a phenylselenyl radical generated by photolysis of diphenyldiselenide, followed by capture of the resultant carbon radical with diphenyldiselenide to give the thermodynamically more stable *trans*-decalin **10**. As only the carbon–selenium bond is cleavable under the irradiation conditions, the *trans* configuration of compound **10** suggested that major isomer

Table 1. Visible-light-mediated seleno transfer radical cyclization of **7**.

Entry	Additive	*T* [°C]	*t*	Yield [%]	**8a**:**8b**
1	no	0–5	3 h	30	3:1
2	0.2 equiv $(PhSe)_2$	0–5	3 h	88	3:1
3	0.2 equiv $(PhSe)_2$	reflux	70 min	90	2:1

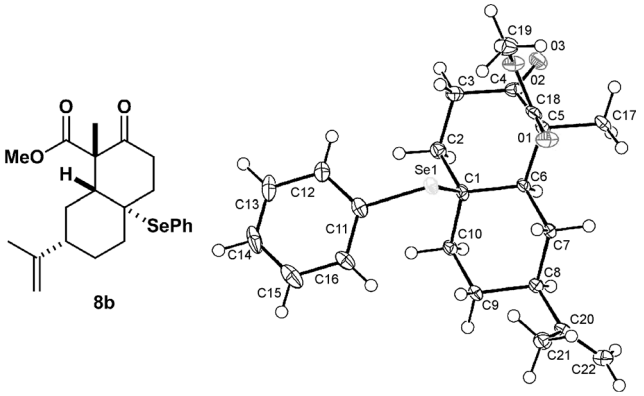


Figure 2. X-ray crystallographic structure of minor isomer **8b** with thermal ellipsoids at 50 % probability levels.

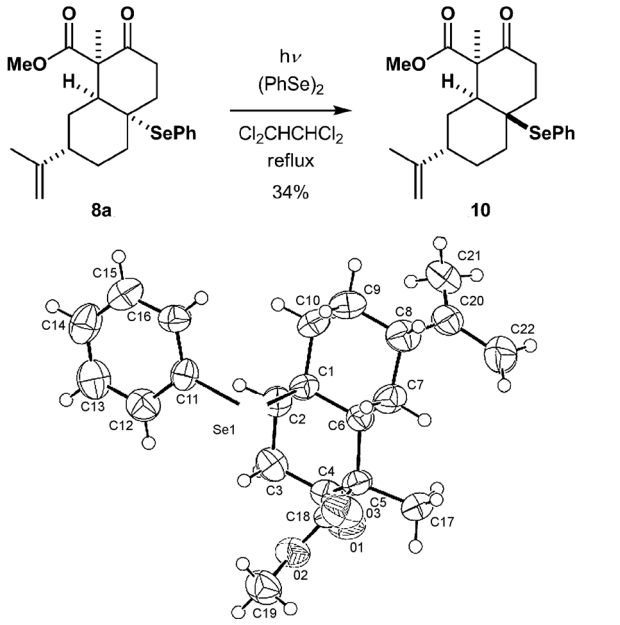
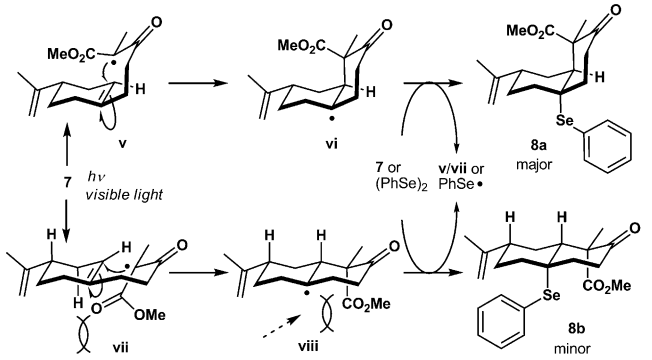


Figure 3. Production of *trans*-decalin **10** from **8a** via epimerization of the selenylated carbon and its X-ray structure with thermal ellipsoids at 50% probability levels.



Scheme 3. Plausible mechanism for the production of selenides **8a** and **8b**.

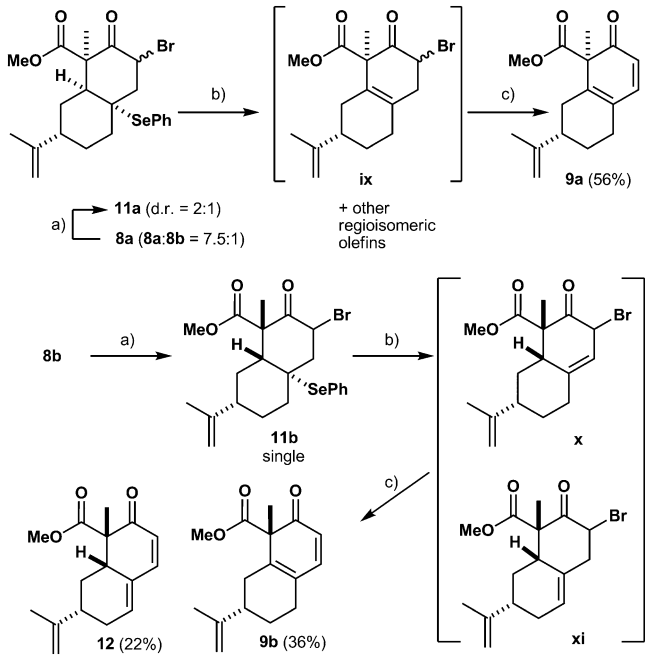
8a originally produced by the radical cyclization possessed the *cis*-decalin structure.

The preferential formation of *cis*-configurational decalin **8a** over *trans*-congener **8b** suggested that the visible-light-mediated reaction favored kinetic control (Scheme 3). As evidenced by the fact that the seleno transfer cyclization took place in the absence of diphenyldiselenide, albeit in poor yield (see above), the carbon–selenium bond of substrate **7** was indeed cleavable by photolysis, generating carbon radicals (**v**/**vii**) stabilized by the two carbonyls. The orientation of the two carbonyl groups of resultant radical (**v**/**vii**) was likely due to the alleviation of their dipolar interaction. The carbon radical further underwent *6-endo* mode cyclization on the double bond to provide a tertiary radical that captured a phenylselenyl group from another substrate **7**, thereby creating a radical chain pathway. In the presence of catalytic diphenyldiselenide, however, the cyclization was accelerated by facilitating the radical chain propagation through efficient capture of the tertiary radical intermediates (**vi**/**viii**) with diphenyldiselenide.[17] It is also likely that the visible-light irradiation of diphenyldiselenide generated phenylselenyl radical[18] that efficiently produces radical intermediates (**v**/**vii**) via S_H2 reaction with **7** to promote the cyclization. Although seemingly the less stable *cis*-isomer **8a** was predominantly produced, this could be rationalized by considering the steric interaction between the methoxycarbonyl substituent and the allylic hydrogen atom as exemplified in **vii**, which underwent flipping to **v** that eventually produced *cis*-selenide **8a** rather than *trans*-isomer **8b**. Furthermore, the 1,3-diaxial interaction between the methoxycarbonyl group and the phenylselenyl donors (**7** or diphenyldiselenide) in transient intermediate **viii** could retard radical trapping and facilitate ring opening to give **v** via **vii**, thus leading to the preferential production of **8a**.

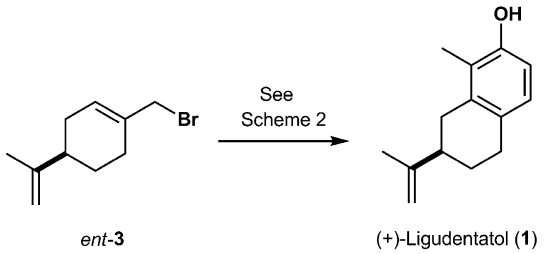
The next task was to aromatize cyclized products **8a** and **8b** to furnish the phenol motif by oxidative functionalization of the B ring of the decalins. Firstly, a mixture of the two decalins **8a**/**8b** (d.r. = 3:1) was subjected to bromination with LDA/NBS in THF at −78 °C to furnish α-brominated compounds as a diastereomeric mixture. Then, hydrogen peroxide (H_2O_2)/pyridine were added to the crude mixture followed by DBU (DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene) to produce desired dienone **9** (d.r. ≈ 3.6:1) in 50% yield over two steps via concomitant selenoxide–hydrogen bromide eliminations. To ensure the complete conversion of all the diastereomeric bromides, DBU was employed to enhance the dehydrobromination. As expected, the *cis*-configuration of the decalin architecture of major isomer **8a** allowed the preferential formation of internal tetrasubstituted olefin **ix** over other regioisomeric olefins via *syn*-elimination mechanisms (Scheme 4): bromination of diastereomerically enriched selenide **8a** (**8a**:**8b** = 7.5:1) with NBS followed by oxidation with H_2O_2/pyridine/DBU afforded exclusively dienone **9a** (56%), whereas minor isomer **8b** under the same conditions gave dienone **9b** (36%) along with regioisomeric olefin **12** (22%). Careful examination of dienone formation from **8b** revealed that **9b** was formed via **x**, which underwent dehydrobromination via deprotonation at the δ-position. Nevertheless, it is worthy to note that both **8a** and **8b** in those transformations could be converted into dienones **9a** and **9b**, respectively.

The end game in the total synthesis of (−)-ligudentatol (*ent*-**1**) involved a facile aromatization-driven demethoxycarbonylation of dienone **9**. Dienone **9** (d.r. = 3.6:1) was heated in wet DMSO in the presence of NaCl under microwave irradiation (200 °C) to efficiently furnish (−)-ligudentatol (*ent*-**1**) in 82% yield ($[\alpha]_D^{25} = -80.8$ ($c = 0.325$, $CHCl_3$); the reported value for (+)-**1** is $[\alpha]_D^{22} = +82.4$ ($c = 0.80$, $CHCl_3$)).[1] The same synthetic protocol using an enantiomer of ketoester **7** available from (*R*)-perillyl bromide (*ent*-**3**) provided access to natural (+)-ligudentatol (**1**) ($[\alpha]_D^{24} = +83.0$ ($c = 0.125$, $CHCl_3$); Scheme 5).

With these enantiomerically pure (+)- and (−)-ligudentatol (**1**) in hand, their antiproliferative activities were evaluat-



Scheme 4. Sequential dienone formation from diastereomeric selenides **8a** and **8b**. Reagents and conditions: a) LDA, NBS, THF, −78 °C; b) H_2O_2, pyridine, THF, rt; c) DBU, rt.



Scheme 5. Total synthesis of (+)-ligudentatol (**1**).

Table 2. IC_{50} values (μM) of (+)-ligudentatol (**1**) and (−)-ligudentatol (*ent*-**1**) against cancer cell lines.

Compound	Cytotoxicity (IC_{50}, μM)			
	S180	PANC-1	HeLa	DU145
(+)-ligudentatol (**1**)	27.5	34.7	42.5	40.3
(−)-ligudentatol (*ent*-**1**)	26.6	32.7	27.9	36.0

ed against several cancer cell lines, including mouse sarcoma (S180), human pancreatic carcinoma (PANC-1), human cervical cancer (HeLa), and human prostate cancer (DU145) (Table 2). The evaluation revealed that both compounds exerted similar, moderate antiproliferative activities against all the tested cancer cells, with IC_{50} values ranging from 26.6 to 42.5 μM, suggesting their potential application in medicinal research.

In conclusion, we have established a new expeditious access to the enantiomers of the norsesquiterpene ligudentatol, which involved a sequential seleno transfer reaction and aromatization protocol. The present chemical synthesis has also allowed us to uncover the antiproliferative activities of both natural and unnatural ligudentatol, adding a new dimension to the development of phenolic medicinal resources.

Experimental Section

The synthetic procedures and the characterization of the compounds studied herein can be found in the Supporting Information.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT). G.A.I.M. acknowledges a scholarship awarded by the Egyptian Ministry of Higher Education for his graduate study.

Keywords: cytotoxicity · natural products · radical reactions · seleno transfer · total synthesis

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[15] CCDC 981449 (**8b**) contains the supplementary X-ray 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/data_request/cif.

[16] CCDC 980715 (**10**) contains the supplementary X-ray 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/data_request/cif. The poor chemical yield of isomerized material **10** from compound **8a** (a diastereomerically enriched material with **8a**:**8b** ratio = 7.5:1) is attributed to the concomitant formation of a tetra-substituted alkene (24%), which was likely produced by elimination of the phenylseleno group during the isomerization process. The unreacted **8b** was also recovered.

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Received: January 23, 2014
Published online: April 2, 2014

