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Highly Efficient and Diastereoselective Synthesis of (+)-Lineatin

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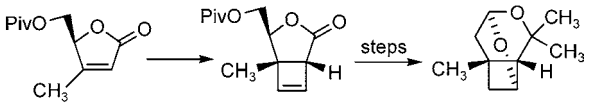
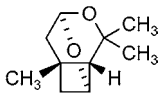
ABSTRACT



A linear sequence was used to synthesize (+)-lineatin in 14 steps and 14% overall yield from a homochiral 2(5*H*)-furanone. Key steps of this synthetic approach feature the diastereoselective construction of a cyclobutene through a photochemical [2 + 2] cycloaddition and a regiocontrolled oxymercuration reaction.

(+)-Lineatin, **1**, is the most important constituent of the aggregation pheromone isolated from the frass of the female ambrosia beetle *Trypodendron lineatum* Olivier, which is a deleterious pest to coniferous forests in Europe and North America (Figure 1).[1]



(+)-Lineatin, **1**

Figure 1.

In the past two decades, this cyclobutane monoterpene has attracted the attention of many synthetic chemists.[2,3] Among the large number of syntheses of lineatin published to date, only a few were devised to provide the pure (+)-enantiomer[3] and, with a unique exception,[3d] they all required resolution steps. Furthermore, the yields achieved in these syntheses were very low (0.2−4%).

Its intriguing structural features, its significant biological activity, and our previous experience in developing syntheses of other naturally occurring cyclobutane pheromones[4] prompted us to select (+)-lineatin as a synthetic target. In this letter we present a highly stereoselective synthesis of this molecule that is superior to previous approaches and proceeds from a readily available chiral 2(5*H*)-furanone as starting material.

Our synthetic strategy takes advantage of the easy and diastereoselective preparation of cyclobutenes through a novel methodology recently developed in our laboratories.

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(1) MacConnell, J. G.; Borden, J. H.; Silverstein, R. M.; Stokkink, E. *J. Chem. Ecol.* **1977**, *3*, 549−561.

(2) Racemic lineatin: (a) Mori, K.; Sasaki, M. *Tetrahedron Lett.* **1979**, 1329−1332. (b) McKay, W. R.; Ounsworth, J.; Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1982**, *60*, 872−880. (c) White, J. D.; Avery, M. A.; Carter, J. P. *J. Am. Chem. Soc.* **1982**, *104*, 5486−5489. (d) Skattebøl, L.; Strestrøm, Y. *Tetrahedron Lett.* **1983**, *24*, 3021−3024. (e) Johnston, B. D.; Slessor, K. N.; Oehlschlager, A. C. *J. Org. Chem.* **1985**, *50*, 114−117. (f) Skattebøl, L.; Stenstrøm, Y. *Acta Chem. Scand., Ser. B* **1985**, *39*, 291−304. (g) Aljancic-Solaja, I.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1987**, *70*, 1302−1307. (h) Kametani, T.; Toya, T.; Ueda, K.; Tsubuki, M.; Honda, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2433−2438. (i) Baeckström, P.; Li, L.; Polec, I.; Unelius, C. R.; Wimalasiri, W. R. *J. Org. Chem.* **1991**, *56*, 3358−3362. (j) Confalonieri, G.; Marotta, E.; Rama, F.; Righi, P.; Rosini, G.; Serra, R.; Venturelli, F. *Tetrahedron* **1994**, *50*, 3235−3250.

(3) (+)-Lineatin: (a) Mori, K.; Sasaki, M. *Tetrahedron* **1980**, *36*, 2197−2208. (b) Slessor, K. N.; Oehlschlager, A. C.; Johnston, B. D.; Pierce, H. D.; Grewal, S. K.; Wickremesinghe, L. K. G. *J. Org. Chem.* **1980**, *45*, 2290−2297. (c) Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron* **1983**, *39*, 1735−1743. (d) Kandil, A. A.; Slessor, K. N. *J. Org. Chem.* **1985**, *50*, 5649−5655. (e) Mori, K.; Nagano, E. *Liebigs Ann. Chem.* **1991**, 341−344.

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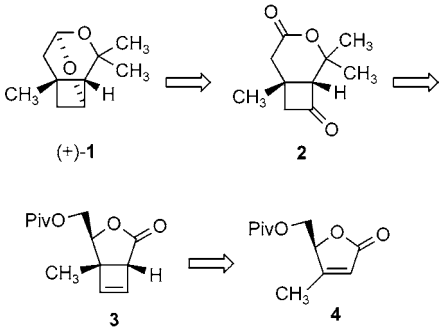
This involves the photochemical reaction of 2(5*H*)-furanones with 1,2-dichloroethylene followed by reductive elimination of chlorine.[5]

Thus, our retrosynthetic analysis of (+)-**1** (Scheme 1) proceeded by initial disconnection of the ketal moiety and

Scheme 1. Retrosynthetic Analysis

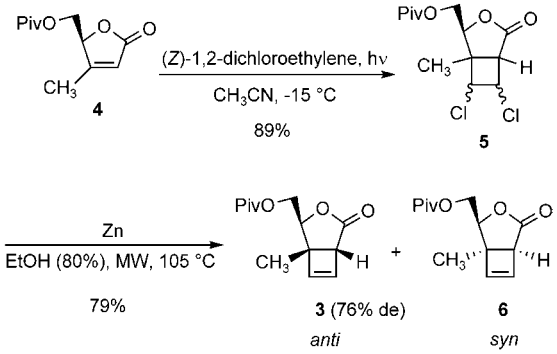


unraveling the keto lactone **2**, whose conversion into **1** has been previously reported.[2e−g,3e] We envisaged that the ketone functionality present in the cyclobutane ring would be regioselectively introduced from a double bond. Given our previous studies on (+)-grandisol,[4] which is structurally related to the present target, we traced the ketone **2** back to the bicyclic lactone **3**, which in turn could be obtained from the appropriate homochiral 2(5*H*)-furanone **4** by a [2 + 2] photocycloaddition to acetylene or some other synthetic equivalent. Therefore, a key step in our approach was our diastereoselective construction of the cyclobutene ring. Another major challenge was the subsequent regioselective oxidation of the double bond in **3**.

2(5*H*)-Furanone **4** had previously shown good facial discrimination in its photocycloaddition to tetramethylethylene, ethylene, and vinylene carbonate.[6] Compound **4** is prepared in three steps and 75% yield from commercially available (*S*)-5-hydroxymethyl-2(5*H*)-furanone according to our previously reported procedure.[7]

Our initial effort focused on the preparation of the key cyclobutene unit **3**. This compound was synthesized by photochemical [2 + 2] cycloaddition of acetylene to **4** in only 23% yield.[8] Fortunately, our novel two-step procedure of the photochemical reaction of **4** with (*Z*)-1,2-dichloroethylene, followed by reductive elimination of chlorine, provided a more effective solution to the problem of accessing compound **3** (Scheme 2).

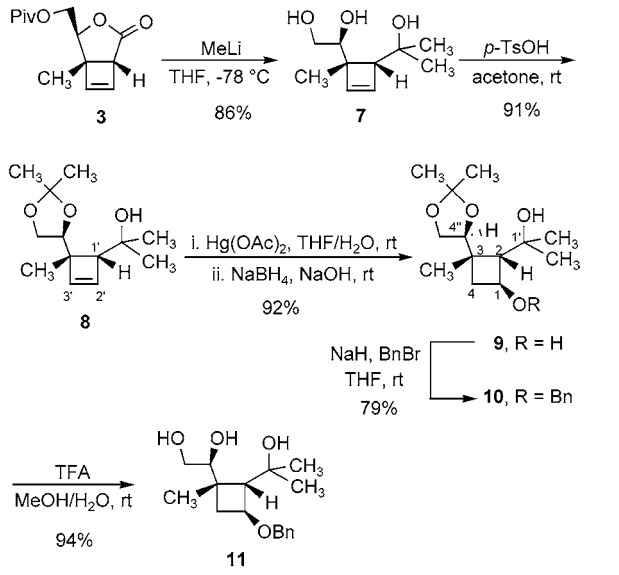
Scheme 2



Thus, irradiation of lactone **4** with (*Z*)-1,2-dichloroethylene in acetonitrile through a quartz filter with a high-pressure mercury lamp for 7.5 h furnished a mixture of seven stereoisomeric cycloadducts **5** in a combined 89% yield. Reductive dehalogenation of this mixture proceeded readily under microwave irradiation[9] giving better yields in much shorter times, compared to the classical thermal conditions.[5] Hence, when the mixture of dichlorocyclobutane isomers **5** was treated with activated Zn in aqueous EtOH in a sealed vessel at 105 °C in a focused microwave reactor for 20 min, a separable mixture of the known cyclobutenes **3** and **6** was obtained in 79% yield and a ratio 88:12. As a result, the pivotal cyclobutene **3** was now available in 61% yield from lactone **4**.

This outstanding improvement in the preparation of **3** led us to proceed further with our proposed synthetic sequence to (+)-lineatin (Scheme 3). Treatment of **3** with an excess

Scheme 3



(4) (a) Alibés, R.; Bourdelande, J. L.; Font, J.; Parella, T. *Tetrahedron* **1996**, *52*, 1279−1292. (b) de March, P.; Figueredo, M.; Font, J.; Raya, J.; Alvárez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 2437−2447.

(5) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Rustullet, A.; Alvárez-Larena, A.; Piniella, J. F.; Parella, T. *Tetrahedron Lett.* **2003**, *44*, 69−71.

(6) (a) Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1391−1402. (b) Gregori, A.; Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron Lett.* **1998**, *39*, 6961−6962. (c) Alibés, R.; Bourdelande, J. L.; Gregori, A.; Font, J.; Rustullet, A.; Parella, T. *J. Carbohydr. Chem.* **2003**, *22*, 501−511.

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of MeLi in THF resulted in addition of two methyl groups to the lactone carbonyl carbon and simultaneous removal of the pivaloyl protecting group, providing triol **7** in 86% yield. Protection of the vicinal diol as the isopropylidene acetal **8** was achieved in 91% yield by reaction of **7** with acetone in the presence of *p*-TsOH.

At this juncture, we intended to introduce the O-functionality at C-2′ through an oxymercuration−demercuration process. Our expectation was that either the hydroxyl group and/or the closer oxygen atom of the dioxolane in **8** would coordinate to and guide the Hg^{2+} to the *endo* face of the olefin. A subsequent trans addition of water should then occur at C-2′ due to the steric hindrance exerted by the methyl group attached to the cyclobutane (Figure 2).[10]

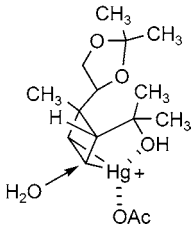


Figure 2. Mercurinium complex.

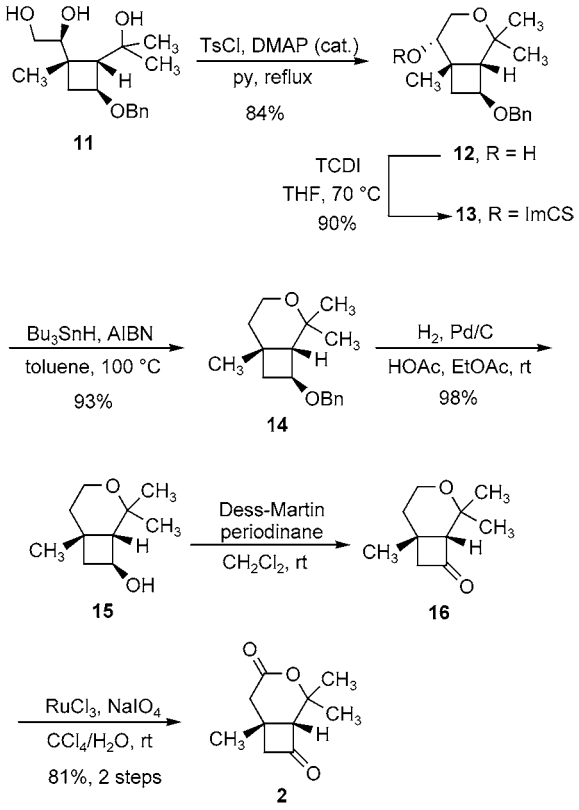
Although the configuration of the new stereogenic center would be opposite to that in the target pheromone, it was envisaged that an inversion could be performed at a later stage of the synthesis through an oxidation−reduction sequence.

To our great satisfaction, when **8** was treated with mercuric acetate in THF/water at room temperature for 2.5 h and demercuration was effected with alkaline sodium borohydride, the alcohol **9** was obtained as a single isomer in 92% yield. The structure and relative stereochemistry of **9** were assigned by one- and two-dimensional NMR techniques. Its regiochemistry was unambiguously proven by an HMBC experiment in which the signal of the angular methyl attached to C-3 showed long-ranged coupling to H-4″, H-2, and one of the protons attached to C-4, while the C-1′ carbon coupled to H-1; this indicated that the hydroxyl group was incorporated at position C-2′ of the cyclobutene **8**. The stereochemistry at the C-1 center of **9** was established on the basis of $^1H/^1H$ correlations observed in the phase-sensitive NOESY spectrum, which showed a correlation between H-4″ and H-1, demonstrating the *exo* orientation of the hydroxyl group.

Next, the secondary alcohol of **9** was selectively benzylated under standard conditions to afford **10**, which after removal of the acetonide protecting group with TFA in a mixture of $MeOH/H_2O$ led to the triol **11** in 94% yield.

Our attention was next directed to construction of the pyran moiety. Thus, triol **11** underwent clean oxycyclization to give **12** in 84% yield upon treatment with TsCl and a catalytic amount of DMAP in refluxing pyridine (Scheme 4). The

Scheme 4



secondary hydroxyl group was then removed by the Barton−McCombie procedure,[11] which involved treating **12** with TCDI in THF and submitting **13** to radical reduction with Bu_3SnH in the presence of AIBN. The desired deoxygenated bicyclic ether **14** was obtained in 84% yield for the two steps.

The final stages of our synthetic approach were as follows. Hydrogenolysis of the benzyl ether from **14** led to the alcohol **15**, which after Dess−Martin (periodinane)[12] oxidation afforded the known and highly volatile bicyclic ketone **16**.[3e] The latter was treated immediately with $RuCl_3/NaIO_4$ in the two-phase system of CCl_4/H_2O to give the keto lactone **2** as a crystalline solid. These transformations all proceeded efficiently, the conversion of **14** into **2** being achieved in

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(12) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

79% overall yield. The physical properties and NMR spectra of **2** matched those previously reported in the literature.[3e] Moreover, our product was found to be enantiomerically pure (>99.5% ee) by chiral GC analysis, $[\alpha]_D$ +209.1 (*c* 0.93, acetone) [lit.[3e] $[\alpha]_D$ +206 (*c* 1.12, acetone)]. The bicyclic keto lactone **2** has previously been transformed into lineatin by double carbonyl reduction with DIBAL-H followed by acid-catalyzed acetalization in 70−74% yield.[2e−g,3e]

In summary, we have reported a new highly stereoselective formal synthesis of (+)-lineatin in an overall yield of 14% starting from furanone **4**. The synthesis is characterized by a diastereoselective photochemical step and a regiocontrolled oxymercuration reaction.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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