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Total Synthesis of (+)-Ligudentatol *via* Photoaddition-Fragmentation-Aromatic Annulation Sequence

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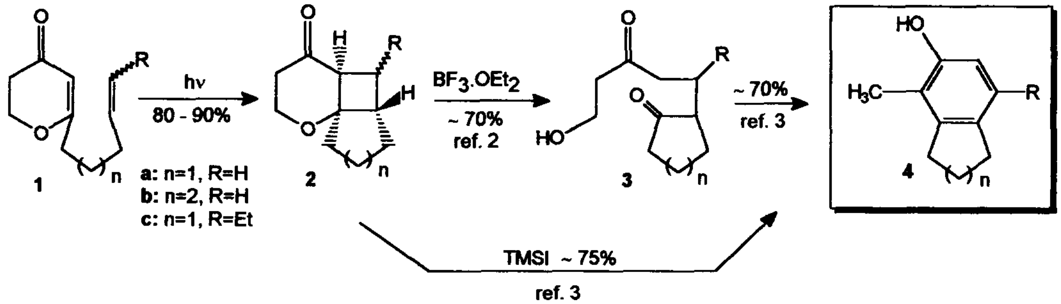
Abstract: First synthesis of the naturally occurring compound (+)-ligudentatol is presented. It demonstrates the synthetic utility of the "Photoaddition-Fragmentation-Aromatic Annulation" sequence, recently developed *via* the intramolecular photocycloaddition of dihydropyrones to alkenes. © 1997 Elsevier Science Ltd.

The synthesis of substituted phenols, fused to aliphatic ring(s) usually starts with the aromatic unit, followed by construction of the remaining aliphatic part. Alternative approaches are based on subsequent construction of the aromatic part *via* intermolecular annulation on substituted cyclic ketones.[1] Most of the approaches derived from both strategies suffer from limitations associated with controlling regioselectivity in the preparation of polysubstituted compounds. Recently, we have developed a versatile and highly regioselective approach for the synthesis of substituted phenols of type 4, fused to aliphatic rings of different sizes. The method based on the sequence of "*Photoaddition-Fragmentation-Aromatic Annulation*" of dihydropyrones[2] of type 1. Two alternative methods provide efficient transformation of the photoproduct(s) to the corresponding phenol.[3] The position of substituents at the aromatic and/or the aliphatic ring(s) can be defined by their corresponding position at the photosubstrate, whereas, the aliphatic ring size (n=1,2) can be determined by the number of carbons connecting the dihydro-4-pyrone to the C=C double bond of the alkenyl side chain in 1.



Scheme 1

Substituted phenolic structures of type 4 can be found in the useful insecticides[4] indan-5-yl-N-methyl-carbamates 5, the phenoxy and alkoxy, di- and tetrahydronaphthalenes of type 6 which are prepared as antagonists of LTD4 and useful as anti-allergy and anti-flammatory agents.[5] It is also found as a substructure in a number of des-A-steroids 7 known as potential anti androgens,[6] the compound with R=Me is considered as one of the most potent compounds with 73% relative binding affinity for the androgen receptor compared to testosterone; and in a number of naturally occurring compounds such as juncunol[7] **8** and the norsesquiterpene (+)-ligudentatol **9**, isolated from the rhizomes of *Ligularia dentata* Hara.[8] We present herein the first synthesis of (+)-ligudentatol (**9**) which demonstrates the synthetic utility of the title sequence.

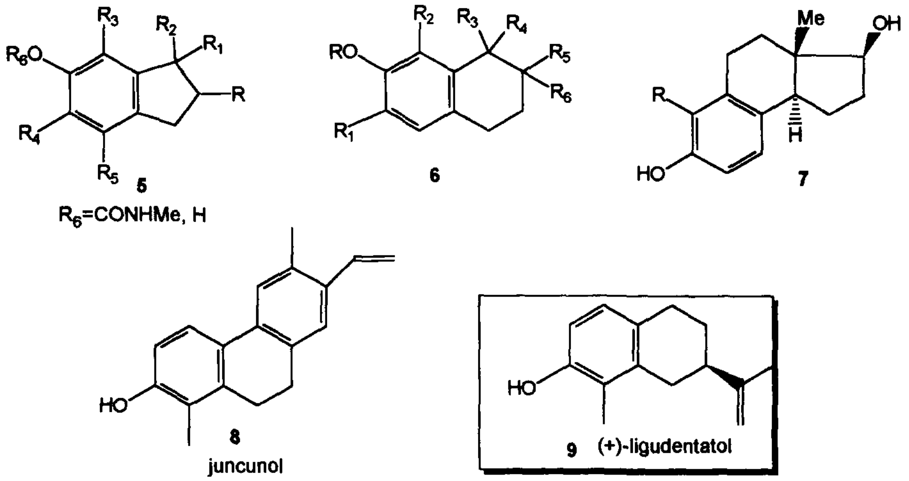
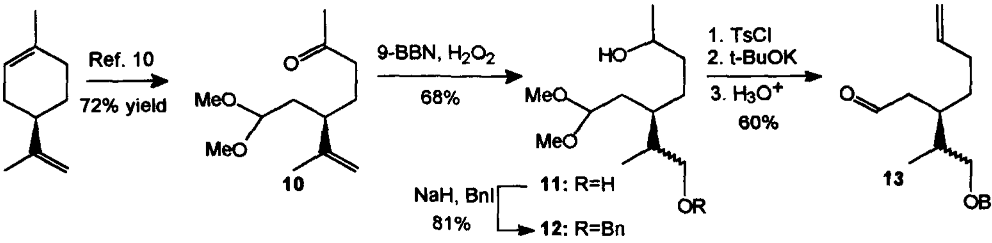


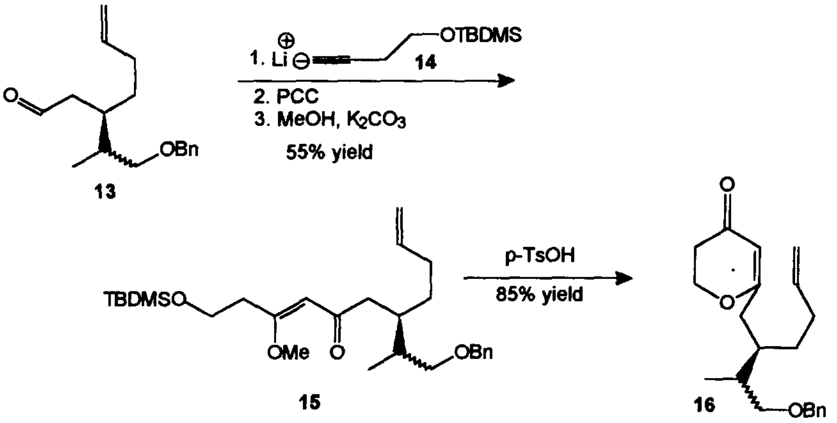
Figure 1

The isopropenyl substituent and its configuration in (+)-ligudentatol could be derived from (+)-limonen. The C=C double bond must be protected in order to preclude its addition to the dihydropyrone at the photocyclo-addition step.[9] The synthesis starts by transforming (+)-limonen to acetal **10**, following the literature procedure.[10] Hydroboration of **10** with 9-BBN[11] afforded the corresponding diol **11** in 68% yield. The primary alcohol in the products mixture was protected as its benzyl ether (BnI, NaH) affording **12** in 81% yield[12]. The secondary alcohol in **12** was transformed to the terminal alkene **13**, needed for the photocyclo-addition to the dihydropyrone. **13** prepared *via* the corresponding tosylate of **12** (TsCl, Pyridin, 0°C), followed by selective elimination with potassium *tert*-butoxide[13] (*tert*-butanol, 60°C), which afforded after hydrolysis of the acetal protection (3N HCl in acetone) the desired aldehyde **13** in 60% yield from **12**.



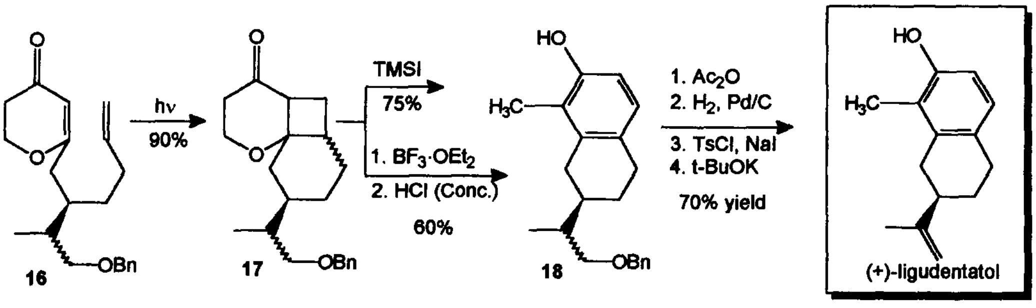
Scheme 2

Aldehyde **13** was transformed to the desired photosubstrates mixture **16** in 47% yield by modification of a reported procedure for the synthesis of 4-pyrones.[14]



Scheme 3

Irradiation of **16** under the usual conditions[15] at 0°C, afforded a mixture of photoproducts **17** in 90% yield. The mixture was transformed to the corresponding phenol products **18** in 75% yield upon treatment with TMSI.[3] Fragmentation of **17** to its corresponding diketoalcohol of type **3** (scheme 1), then aromatic annulation *via* the alternative two step sequence was examined also. Treatment of **17** with borontrifluoroetherate then concentrated hydrochloric acid, afforded **18** in 60% yield. The synthesis of the naturally occurring compound (+)-ligudentatol[16] was completed from **18** by protection of the phenol, reductive cleavage of the benzyl ether followed by elimination of the corresponding iodide and deprotection of the phenol upon treatment with *tert*-BuOK, as described in the following scheme.



Scheme 4

In summary, the first synthesis of the naturally occurring compound (+)-ligudentatol has been achieved. The synthesis demonstrates the utility of the photoaddition-fragmentation-aromatic annulation sequence of dihydro-4-pyrones to alkenes in the regioselective preparation of polysubstituted phenols. The two step sequence (**15** → **17**) afforded the corresponding substituted phenol in over 63% yield.

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(15) Irradiation of **16** (100 mg) was carried out in acetonitrile solution (16 mL) at 0°C, using a 80-W mercury vapor lamp (Q-81) *via* a Pyrex glass filter. The reactions were followed by the UV absorption of **16** on TLC and completed after 1.5 h.

(16) The following spectroscopic data are in full agreement with the reported data of (+)-ligudentatol in ref. 8. ^{13}C-NMR (JMOD-XH) (CDCl$_3$): (+) 151.3, (+) 149.9, (+) 136.5, (+) 128.8, (-) 126.7, (+) 121.8, (-) 112.6, (+) 109.1, (-) 42.1, (+) 32.8, (+) 29.6, (+) 27.8, (-) 20.6, (-) 10.9; HR-MS: Calcd for $C_{14}H_{18}O$: 202.1357 m/z, Found: 202.1345 m/z; $[\alpha]^{20}$ +82.1° (*c* 0.87, CHCl$_3$).

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