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Concise synthesis of anolignan A

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Abstract

An efficient synthesis of anolignan A has been achieved in eight steps in 30% overall yield from piperonal employing TiCl_4 -mediated addition of a 1-trimethylsilyl-2,3-butadiene to an aldehyde as the key step.
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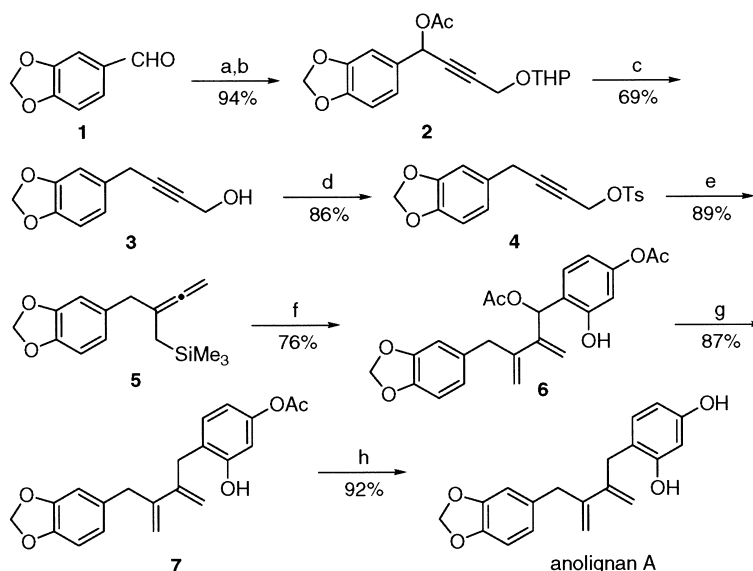
Anolignan A was isolated from *Anogeissus acuminata* as an active HIV-1 reverse transcriptase inhibitory constituent by bioassay-guided fractionation.¹ Recently, we have developed an efficient method for the preparation of substituted 1,3-butadienes employing 1-trimethylsilyl-2,3-butadienes.^{2,3} The characteristic unsymmetrical 2,3-disubstituted 1,3-butadiene structure as well as its interesting biological activity prompted us to investigate a total synthesis of anolignan A based on this methodology. We report herein the first synthesis of anolignan A.

Piperonal **1** was first converted into propargyl alcohol **3** via acetate **2** by a three-step sequence involving propargylation using tetrahydro-2-(2-propynyloxy)-2H-pyran, acetylation, and removal of the benzylic acetoxy group with $\text{TFA-Et}_3\text{SiH}$ in 65% overall yield. Several attempts to obtain **3** by direct alkylation of tetrahydro-2-(2-propynyloxy)-2H-pyran with piperonyl chloride failed. After tosylation of **3**, reaction³ of tosylate **4** with trimethylsilylmethylmagnesium chloride in the presence of CuCN and LiCl produced 1-trimethylsilyl-2,3-butadiene **5** selectively in good yield. TiCl_4 -mediated addition of **5** to 2,4-diacetoxybenzaldehyde in the presence of acetonitrile (1 equiv.) proceeded smoothly with concomitant acyl migration to give 1,3-butadiene **6**. In this particular case, addition of acetonitrile was found to be of critical importance for this successful transformation, because compound **6** was not obtained in the absence of acetonitrile.[†] Possibly the Lewis acidity of TiCl_4 was appropriately attenuated by complexation with acetonitrile so that

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† Reaction of benzaldehyde with 1-trimethylsilyl-2,3-butadiene was found to be unsuccessful when TiCl_4 was used as the catalyst alone, see: Hatakeyama, S.; Sugawara, K.; Kawamura, M.; Takano, S. *Tetrahedron Lett.* **1991**, 32, 4509–4512.

the resulting acid-labile **6** was obtained without decomposition. Upon treatment of **6** with $\text{HCO}_2\text{H}-\text{Et}_3\text{N}$ in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ (3 mol%) in boiling dioxane,⁴ the reductive removal of the benzylic acetoxy group took place with complete regioselectivity to give **7** exclusively. Finally, saponification of **7** furnished anolignan A as colorless needles, mp 97–98°C (CH_2Cl_2),[‡] which exhibited spectral properties (^1H and ^{13}C NMR, IR, MS) in accord with those¹ reported (Scheme 1).



Scheme 1. *Reactions and conditions:* (a) tetrahydro-2-(2-propynyloxy)-2H-pyran, *n*-BuLi, THF, -78°C ; (b) Ac_2O , Et_3N , DMAP, CH_2Cl_2 ; (c) Et_3SiH , TFA, CH_2Cl_2 , -20°C ; (d) *n*-BuLi, TsCl, THF, -40°C ; (e) $\text{Me}_3\text{SiCH}_2\text{MgCl}$ (3 equiv.), CuCN (3 equiv.), LiCl (6 equiv.), THF, -40°C ; (f) 2,4-diacetoxybenzaldehyde, TiCl_4 (1 equiv.), CH_3CN (1 equiv.), CH_2Cl_2 , -78°C ; (g) HCOOH (10 equiv.), Et_3N (10 equiv.), $\text{PdCl}_2(\text{PPh}_3)_2$ (3 mol%), dioxane, reflux; (h) 5% NaOH, MeOH

In conclusion, the present work illustrates a new methodology for the synthesis of dibenzyl-butadiene lignans as well as the synthetic utility of 1-trimethylsilyl-2,3-butadienes.

Acknowledgements

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[‡] The melting point was not reported in the literature.