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Total Synthesis of (±)-Hedychilactone B: Stepwise Allenoate Diene Cycloaddition To Prepare Trimethyldecalin Systems

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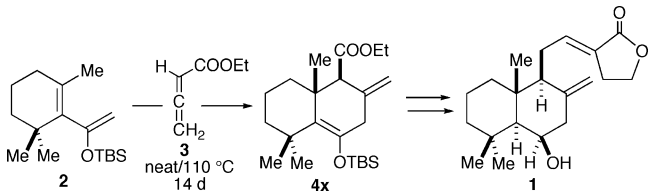
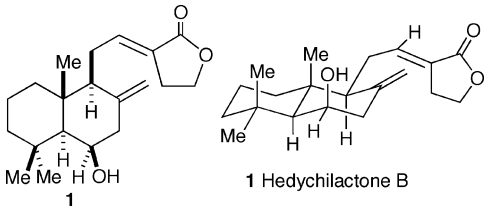
ABSTRACT



The total synthesis of the diterpene hedychilactone B 1 is reported. The exo adduct 4x, the major product of the stepwise [4+2] cycloaddition of the diene 2 and the allenoate 3, has been converted into 1 via 7 steps, among them a key nonconjugative hydrolysis of a γ-methylene silyl enol ether and an *E*-selective olefination.

Hedychilactone B **1** (Scheme 1), a labdane diterpene isolated from various types of Zingiberaceae plants, e.g., *Hedychium coronarium* Koen, has anti-inflammatory activity and has shown strong inhibition of nitric oxide production (IC_{50} 28 μM).[1] No synthesis of this lactone has appeared in the literature to date. Recently we reported the preparation of very hindered trimethyldecalin systems, involving a novel stepwise [4+2] cycloaddition of the very hindered diene **2** with the allene carboxylate **3** to give the [4+2] cycloadducts **4xn** by a mechanism that proceeds via the cyclobutane **5**, the initial [2+2] cycloadduct.[2] We report here the total synthesis of hedychilactone B **1** from the exo [4+2] cycloadduct **4x** via a key nonconjugative hydrolysis of a γ-methylene silyl enol ether and an *E*-selective olefination to install the desired *E*-alkylidene lactone.

Scheme 1



As we reported earlier, the trimethylcyclohexenyl diene **2** was prepared from 2,6-dimethylcyclohexanone in six steps and 51% overall yield: methylation, Barton vinyl iodide formation[3] (via the corresponding hydrazone), trapping of

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(2) Jung, M. E.; Murakami, M. *Org. Lett.* **2006**, *8*, 5857−5859.

(3) (a) Barton, D. H. R.; Bashiardes, G.; Fourrey, J. L. *Tetrahedron Lett.* **1983**, *24*, 1605−1608. (b) Kende, A. S.; Deng, W.-P.; Zhong, M.; Guo, X.-C. *Org. Lett.* **2003**, *5*, 1785−1788. (c) Di Grandi, M. J.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989−4992. (d) Pazos, Y.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **2001**, *66*, 8483−8489. (e) Helliwell, M.; Thomas, E. J.; Townsend, L. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1286−1296. (f) Jung, M. E.; Duclos, B. A. *Tetrahedron* **2006**, *62*, 9321−9334.

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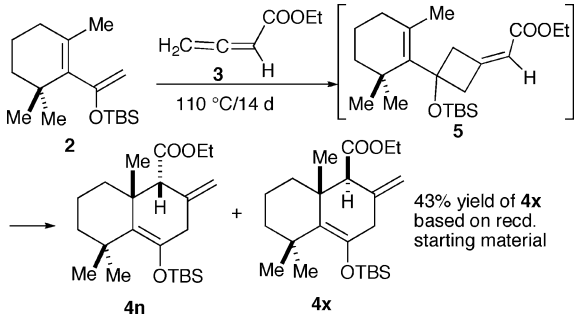
the derived vinyllithium with acetaldehyde, oxidation, and final silyl enol ether formation. Heating a neat mixture of the diene **2** with the allene carboxylate **3** (prepared in 58% yield by reaction of ethoxycarbonylmethylenephosphorane with acetyl chloride)[4] at 110 °C for 14 d gave a separable mixture of three products, the [2+2] cycloadduct **5**, the desired exo [4+2] cycloadduct **4x**, and the endo adduct **4n** in 9%, 23.3%, and 11.7% yield, respectively (Scheme 2),

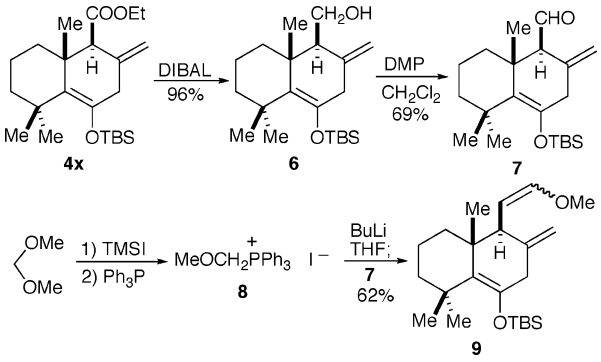
Scheme 2



with 31% of the recovered starting diene **2**. The cyclobutane **5** could be converted into the same 2:1 ratio of **4x** and **4n**, resulting in a 43% overall yield of **4x** based on recovered starting material.

The conversion of the adduct **4x** into hedychilactone B **1** required two key steps: formation of the axial cyclohexanol without moving the *exo*-methylene unit into the more stable endocyclic position and extension of the side chain to give the *E*-alkylidene lactone. To hydrolyze the silyl enol ether group and reduce the ketone functionality without disrupting the exocyclic methylene unit and the side chain functionality, we decided to extend the side chain and protect it in one inclusive process. Reduction of the ester **4x** with DIBAL afforded the alcohol **6**, which was oxidized under Dess–Martin periodinane conditions to afford the aldehyde **7** in good yield (Scheme 3). Formation of the ylide from the

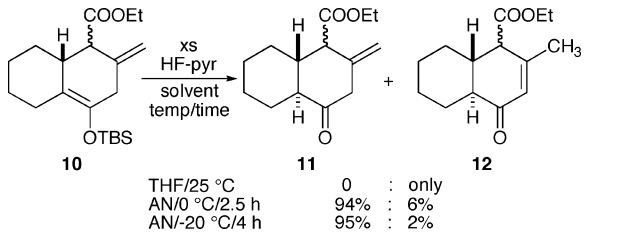
Scheme 3



methoxymethylphosphonium salt **8**,[5] prepared in two steps from methylal via reaction with trimethylsilyl iodide (TMSI) and triphenylphosphine, by reaction with *n*-butyllithium and addition of the aldehyde gave an approximately 2:1 ratio of stereoisomers of the enol methyl ether **9** in 62% yield.

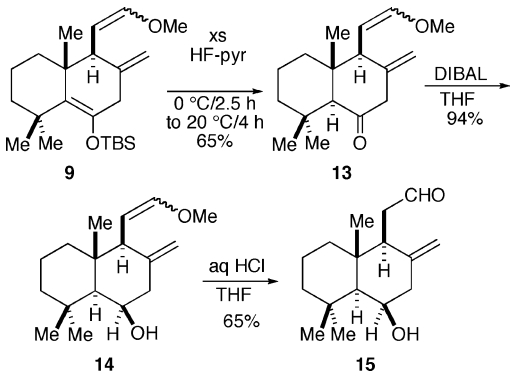
The key step of hydrolysis of the silyl enol ether without concomitant conjugation of the exocyclic methylene unit was first tested on a model system, namely the mixture of endo and exo esters **10** (prepared by a formal [3,3] sigmatropic shift of the methylene cyclobutane as we reported earlier).[6] Treatment of the silyl enol ether **10** with HF–pyridine under various conditions gave a mixture of the desired nonconjugated enone **11** along with the undesired conjugated enone **12** (Scheme 4). The use of acetonitrile as the solvent and

Scheme 4



low temperature greatly favored the desired product **11** while tetrahydrofuran (THF) and higher temperatures led to the more stable enone **12**. When these conditions were applied to the real system, similar results were obtained in that treatment of **9** gave a 65% yield of the desired *trans*-decalone **13** while the exocyclic methylene remained untouched (Scheme 5). As expected, reduction of the decalone with

Scheme 5



DIBAL occurred from the less-hindered equatorial direction to give the desired axial alcohol **14** in 94% yield. No protection of this alcohol was required to finish the synthesis. Very mild acidic hydrolysis of the methyl enol ether (aq HCl in THF) afforded the aldehyde **15** in 65% yield.

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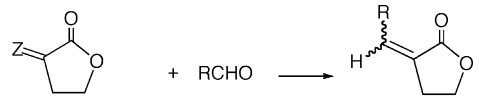
(5) Jung, M. E.; Mazurek, M. A.; Lim, R. M. *Synthesis* **1978**, 588–590.
(6) (a) Jung, M. E.; Nishimura, N.; Novack, A. R. *J. Am. Chem. Soc.* **2005**, *127*, 11206–11207. (b) Novack, A. R. Ph.D. Thesis, UCLA, 2005.

Formation of the *E*-double bond between the butyrolactone unit and the aldehyde of the side chain was all that was required to complete the synthesis. Here again we first looked at this reaction in a model series (Table 1). Following the work of Wiemer,[7] we treated the diethylphosphono lactone **16** with KHMDS and 18-C-6 in THF in the presence of cyclohexanecarboxaldehyde **17** and isolated a mixture of alkenes, in which the *Z*-isomer **18*Z*** predominated over the desired *E*-isomer **18*E***. Addition of potassium *tert*-butoxide gave an even greater preponderance of the *Z*-isomer. Since Wiemer had used the simple acyclic aldehyde propanal, we repeated these experiments using butanal **19** and again obtained largely the same results, namely a preference for the *Z*-isomer **20*Z***. Consequently we switched to the triphenylphosphoranylidenelactone **21**[8] and obtained the desired *E*-isomers **18*E*** and **20*E*** with very good selectivity. The structures of the products were determined by chemical shifts of olefinic protons, namely the proton in the *E*-isomer absorbs at δ ~6.6−6.7 whereas the corresponding proton in the *Z*-isomer absorbs at δ ~6.0−6.2.[9] We cannot explain the differences in our results and those of Wiemer.

Table 1. Stereoselectivity in Lactone Olefinations



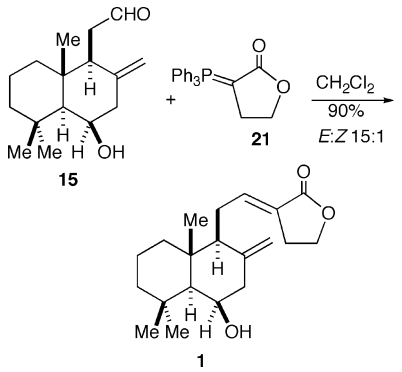
16 Z = $PO(OEt)_2$, H **17** R = Cy **18** R = Cy
21 Z = PPh_3 **19** R = Pr **20** R = Pr

reagent	RCHO	base/solvent	*E*:*Z* ratio
16	**17**, R = Cy	KMHDS/18-C-6/THF	1:23
16	**17**, R = Cy	KMHDS/18-C-6/THF[a]	1:32
16	**19**, R = Pr	KMHDS/18-C-6/THF	1:18
21	**17**, R = Cy	$CHCl_3$	40:1
21	**19**, R = Pr	$CHCl_3$	100:1

[a] KO*t*Bu added.

As shown in Scheme 6 the synthesis of hedychilactone B **1** was completed by treating the aldehyde **15** with the triphenylphosphoranylidenelactone **21** in dichloromethane to afford a 90% yield of the desired natural product as a 15:1 *E*:*Z* ratio. The proton and carbon NMR data matched exactly those reported in the literature for this compound.[1b]

Scheme 6



Thus, we have carried out the first total synthesis of the biologically active diterpene hedychilactone B **1** from the [4+2] cycloadduct **4x** formed in 43% yield via a stepwise cycloaddition of a very hindered diene and an allenoate dienophile. The key steps involved a nonconjugative hydrolysis of a γ-methylene silyl enol ether and the highly stereoselective olefination of the side-chain aldehyde to give predominately the *E*-alkylidene lactone. Studies of further uses of the stepwise [4+2] cycloaddition in terpene synthesis are underway in our laboratories and will be reported in due course.

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

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