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Total Synthesis of (±)-Hedychenone: Trimethyldecalin Terpene Systems via Stepwise Allenoate Diene Cycloaddition

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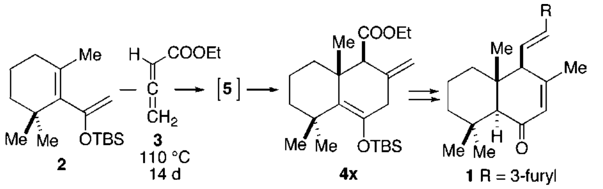
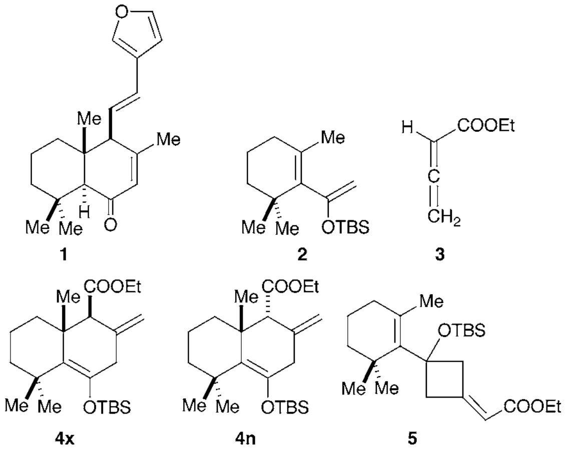
ABSTRACT



The total synthesis of hedychenone 1 is described. The cycloaddition of the hindered diene 2 and the allenecarboxylate 3 has been shown conclusively to proceed via the [2+2] cycloadduct 5 to give a 2:1 mixture of the desired formal Diels–Alder adducts, the exo and endo isomers 4xn and is thus a stepwise [4+2] cycloaddition. The exo isomer 4x was converted in four steps (reduction, oxidation, olefination, and desilylation) into hedychenone 1.

Hedychenone **1**, a labdane diterpene isolated from various types of Zingiberaceae plants, e.g., *Hedychium coronarium* Koen., has shown very strong inhibition of nitric oxide production (IC$_{50}$ of 7.9 μM), has antiinflammatory activity, and also inhibits the release of β-hexosaminidase and thus is antiallergic (Scheme 1).[1] No total synthesis of this enone has been reported, although a synthesis from the naturally occurring diterpene diol larixol has appeared in the literature.[2] Recently, we have shown that very hindered cyclohexene systems can be prepared either by a direct [4+2] cycloaddition catalyzed by a mixed Lewis acid[3] or via the formal [3,3]-sigmatropic rearrangement of 1-alkenyl-3-alkylidenecyclobutyl silyl ethers.[4] We report here 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 initial [2+2] cycloadduct, the cyclobutane **5**.

Scheme 1



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(1) (a) Sharma, S. C.; Tandon, J. S.; Uprety, H; Shukla, Y. N.; Dhar, M. M. *Phytochemistry* **1975**, *14*, 1059−1061. (b) Zhao, Q.; Zou, C.; Hao, X. J.; Chen, Y. Z. *Chin. Chem. Lett.* **1999**, *10*, 531−532. (c) Matsuda, H.; Morikawa, T.; Sakamoto, Y.; Toguchida, I.; Yoshikawa, M. *Heterocycles* **2002**, *56*, 45−50. (d) Matsuda, H.; Morikawa, T.; Sakamoto, Y.; Toguchida, I.; Yoshikawa, M. *Bioorg. Med. Chem.* **2002**, *10*, 2527−2534. (e) Morikawa, T.; Matsuda, H.; Sakamoto, Y.; Ueda, K.; Yoshikawa, M. *Chem. Pharm. Bull.* **2002**, *50*, 1045−1049. (f) Liu, X.-H.; Wang, W.; He, Z.-D.; Wang, H.-Q.; Yang, C.-R.; Chen, B. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1999**, *55*, iii, IUC9900129. (g) Srimal, R. C.; Sharma, S. C.; Tandon, J. S. *Indian J. Pharmacol.* **1984**, *16*, 143−147. (h) Zhao, Q.; Hao, X. J.; Chen, Y. Z.; Zou, C. *Yaoxue Xuebao* **1995**, *30*, 119−122; *Chem. Abs.* **1996**, *123*, 5671.

(2) Aslaoui, J.; Li, H.; Morin, C. *Tetrahedron Lett.* **2005**, *46*, 1713−1716.

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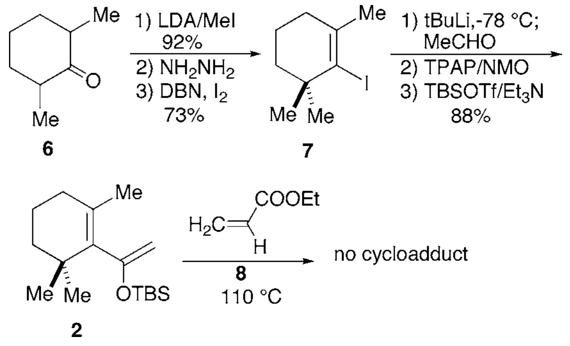
A potentially quite useful route to the trimethyldecalin unit of diterpenes, sesterterpenes, and even triterpenes would be the direct Diels−Alder cycloaddition of a suitably functionalized diene having the trimethylcyclohexane moiety of the A ring with a simple or complex dienophile thereby generating the B ring in one convergent process. There are very few examples of such a strategy being successful, partly because of the steric hindrance involved in such a cycloaddition, but the existence of new methods of carrying out Diels−Alder or Diels−Alder-type reactions argues that this route should be reexamined. The diene for the key cycloaddition, 2-(1-*tert*-butyl-dimethylsilyloxyethenyl)-1,3,3-trimethylcyclohexene **2**, was readily prepared from 2,6-dimethylcyclohexanone **6** in several steps (Scheme 2). Methylation gave the trimethyl ketone (92%) which was then subjected to a Barton vinyl iodination procedure, namely formation of the hydrazone and treatment with iodine and base to give the vinyl iodide **7** in 73% yield for the final two steps. Formation of the vinyllithium with *tert*-butyllithium followed by trapping with acetaldehyde, TPAP/NMO oxidation of the resulting alcohol to the acetyl group, and kinetic silyl enol ether formation afforded the diene **2** in 88% yield from **7**. Heating a neat mixture of the diene **2** and ethyl acrylate **8** afforded none of the desired Diels−Alder adduct giving back only the starting diene and polymeric material. This lack of normal [4+2] cycloaddition reactivity is not at all surprising because theoretical calculations indicate that the diene **2** exists mainly in the noncoplanar conformation **2B** rather than in the cis-planar conformation **2A** required for a concerted [4+2] cycloaddition (Figure 1). Both molecular mechanics and DFT methods indicate that the ground-state twisted conformation, e.g., **2B**, is 9−14 kcal/mol more stable than the cis-coplanar conformation **2A**.[5]

Scheme 2



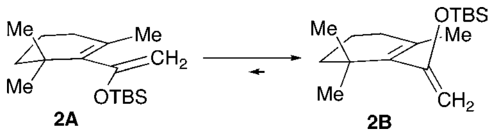
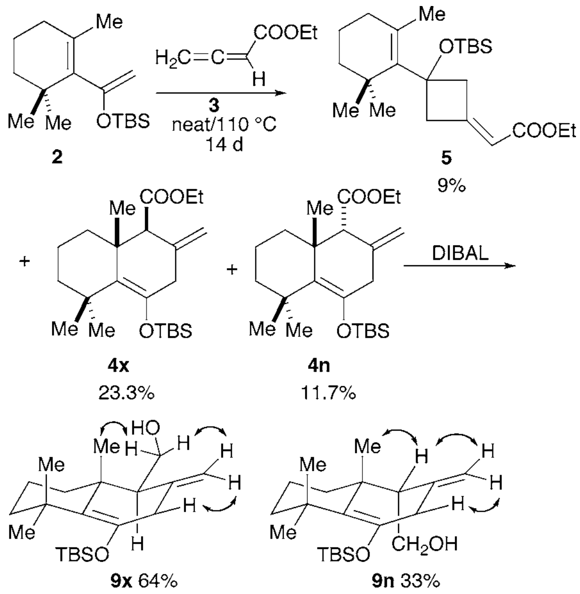


Figure 1. Conformations of diene **2**.

Knowing that the direct [4+2] cycloaddition was very difficult, we decided to see if a stepwise cycloaddition process could be induced to occur, namely an initial [2+2] cycloaddition followed by the [3,3]-sigmatropic rearrangement to produce overall the same product. This is similar to our earlier work[4] where we specifically prepared the cyclobutane from a silyloxydiene and an allene carboxylate. Thus, heating a neat mixture of the allene carboxylate **3** (prepared in 58% yield by reaction of acetyl chloride with ethoxycarbonylmethylenetriphenylphosphorane)[6] with the diene **2** at 110 °C for 14 days gave a separable mixture of three products, the [2+2] cycloadduct **5** in 9% yield, the desired exo [4+2] cycloadduct **4x** in 23.3% yield, and the endo adduct **4n** in 11.7% yield (Scheme 3). This is yet another example of the use of allenes in difficult cycloadditions.[7] In addition to the three cycloadducts, 31% of the starting diene **2** was recovered. The structures of the two [4+2] cycloadducts were determined by NOE experiments on the corresponding alcohols **9xn** (prepared by DIBAL reduction). We believe that the [4+2] cycloadducts **4xn** are formed in a stepwise fashion, namely via the initial formation of **5**, for the following reasons: (1) monitoring the appear-

Scheme 3



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(3) (a) Jung, M. E.; Davidov, P. *Angew. Chem.* **2002**, *41*, 4125−4128. (b) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649−1651.

(4) Jung, M. E.; Nishimura, N.; Novack, A. R. *J. Am. Chem. Soc.* **2005**, *127*, 11206−11207.

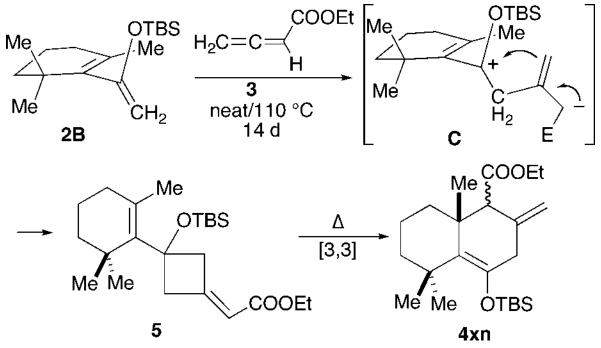
(5) MM2 calculations using Macromodel indicate a difference of about 14 kcal/mol favoring **2B** (the cis planar conformation **2A** was constrained and held for these calculations). DFT calculations using B3LYP/6-31.G*// HF/6−-1.G* indicate a 9.2 kcal/mol difference favoring **2B**, and those using just HF/6-31.G* gave a 12.8 kcal/mol difference.

(6) Paik, Y. H.; Dowd, P. *J. Org. Chem.* **1986**, *51*, 2910.

(7) For allene cycloadditions, see: (a) Jung, M. E.; Min, S.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10834−10835. (b) Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, *121*, 3529−3530. (c) Kanematsu, K. *Rev. Heteroatom Chem.* **1993**, *9*, 231−259. (d) Aso, M.; Kanematsu, K. *Trends Org. Chem.* **1995**, *5*, 157−169. (e) Gras, J. L.; Galledou, B. S.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1988**, *4*, 757−767.

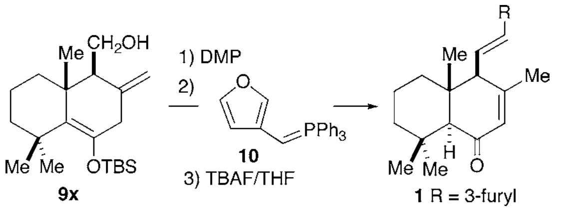
ance of products with time shows that the [2+2] cycloadduct **5** is produced before any of the [4+2] cycloadducts **4xn**, and its concentration decreases with the production of **4xn**; (2) thermolysis of a solution of **5** in toluene (200 °C, μwave) produces an identical 2:1 ratio of **4xn** as does the reaction of **2** and **3**, thereby providing an additional 6% of the exo adduct **4x**; (3) the cycloaddition of the diene **2** and ethyl acrylate **8** does not proceed under the conditions that produce **4xn**; and (4) as mentioned above, theoretical calculations indicate that the diene **2** exists mainly in the noncoplanar conformation **2B** which is unsuitable for the direct [4+2] cycloaddition. Thus, we postulate that the diene **2** reacts via its most stable conformation **2B** with the allene ester **3** via a stepwise mechanism to give first the zwitterion **C** which then closes to the less sterically hindered cyclobutane **5** via trapping of the cation by the unsubstituted end of the allyl anion (Scheme 4). On further heating, **5** rearranges to the observed [4+2] cycloadducts **4xn**. Although at present we cannot explain why the ratio of products does not more greatly favor the exo isomer as it did in other cases,[4,8] we believe that this is the first clear example of a Diels−Alder-like product being produced via a demonstrably nonconcerted pathway which involves the intermediacy of a [2+2] cycloadduct. Even though the yield of this process is somewhat low (overall yield of ~43% of **4x** based on unrecovered starting diene **2** and the separate rearrangement of **5** to **4xn**), the conciseness of this direct approach to trimethyldecalin terpene systems should find use in synthesis.

Scheme 4



Having successfully prepared the desired [4+2] cycloadduct, we finished the synthesis of (±)-hedychenone **1** in three steps (Scheme 5). The primary alcohol **9x**, formed by treatment of **4x** with DIBAL, was oxidized to the aldehyde with Dess Martin periodinane (DMP). Wittig reaction of this aldehyde with the known 3-furyl ylide **10**[9] followed by simple desilylation and in situ conjugation of the unconjugated enone afforded (±)-hedychenone **1**. The proton NMR data of the synthetic material matched that reported for the natural product,[1a] and the carbon NMR spectrum is what would be expected for this structure.[10]

Scheme 5



In summary, we have demonstrated that highly substituted functionalized trimethyldecalin systems common to many terpenes can be prepared directly via a stepwise diene allenoate cycloaddition process. We have also presented strong evidence that the key reaction proceeds via the intermediacy of the [2+2] cycloadduct. The use of this procedure for the synthesis of diterpene natural products is currently under study in our labs.

Acknowledgment. We thank the National Science Foundation (CHE 0314591 and CHE 0614591) for generous support of this work. M.M. thanks Sankyo Co. Ltd. for generous support. We thank Daniel Ess and Dr. Michael Trzoss (UCLA) for their help with the theoretical calculations and Professor Ken Houk (UCLA) for useful discussions.

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

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[8] Indeed, this ratio agrees well with our theoretical calculations of the transition structures and energies for the [3,3]-sigmatropic rearrangement of such [2+2] cycloadducts to the mixture of exo and endo [4+2] cycloadducts. Zhao, Y.-L.; Suhrada, C. P.; Jung, M. E.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 11106−11113.

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[10] Carbon NMR of **1**: δ 199.9, 157.2, 143.6, 140.2, 128.1, 126.0, 124.6, 123.8, 107.4, 63.4, 61.3, 43.3, 42.7, 40.2, 33.6, 32.5, 23.0, 21.7, 18.1, 15.7.