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A Formal Total Synthesis of Dysidiolide

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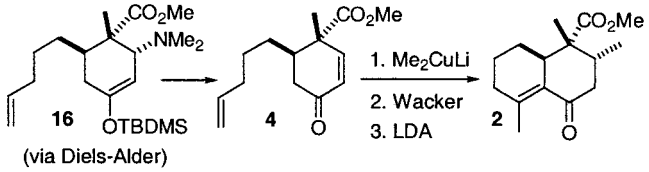
ABSTRACT



A formal total synthesis of the natural product dysidiolide is described. Starting from a Diels–Alder reaction between an enoate and a Rawal diene, the cyclohexenone 4 was synthesized. A subsequent stereospecific methyl cuprate addition established the desired *trans* configuration in the cyclohexane 3. Wacker oxidation of the pentenyl side chain to the diketone 17 followed by an intramolecular aldol condensation led to the bicyclic enone 2, a key intermediate in a recently reported synthesis of dysidiolide.

In the search process for new molecular targets toward the treatment of diseases, the screening of natural products in cells or whole organisms is still an important cornerstone. Since whole cells basically contain a library of targets, this strategy ensures that only promising targets are identified. In addition, the discovery of a new target might offer additional modes of interference by invoking events upstream or downstream of a biological pathway. An interesting case at hand is the C25 isoprenoid compound dysidiolide (**1**) which was found to be an inhibitor of the protein phosphatase cdc25A.[1] Blocking of this enzyme causes arrest of the cell cycle at the G2/M transition, which identified dysidiolide (**1**) and other inhibitors of this enzyme as promising antitumor compounds. Of particular interest in this regard is the fact that cdc25A is overexpressed in a number of tumor cell lines.

Structurally, dysidiolide (**1**) belongs to the group of clerodane di- and sesquiterpenoids.[2] These compounds are characterized by a bicyclo[4.4.0] ring system with an array of four stereogenic centers. While there are many similar compounds known, the relative and absolute stereochemistry and the nature of the side chains in dysidiolide (**1**) are rather unique. Because of the structural features and biological activity, dysidiolide (**1**) has attracted considerable interest. The first total synthesis was patterned along the biosynthetic pathway featuring a methyl shift as the key reaction.[3] For compounds with a cyclohexene substructure, a Diels−Alder approach utilizing a vinylcyclohexene is a more obvious strategy. In fact, four other total syntheses are based either on intermolecular or on intramolecular Diels−Alder reactions of a vinylcyclohexene.[4−7] In addition, a formal total synthesis[8] and some model studies have been reported.[9] We planned to develop a synthetic route that would allow for the introduction of the side chains at a rather late stage, thereby facilitating structure−activity studies. Central to our plan was the introduction of the C15 side chain via a conjugate addition to the convex face of an enone such as **2** (Figure 1). The enone **2** itself would arise from the substituted ketone **3**. One of the substituents flanking the ester group would be introduced through a cuprate addition to an enone **4**. This enone, in turn, could be synthesized by a Diels−Alder

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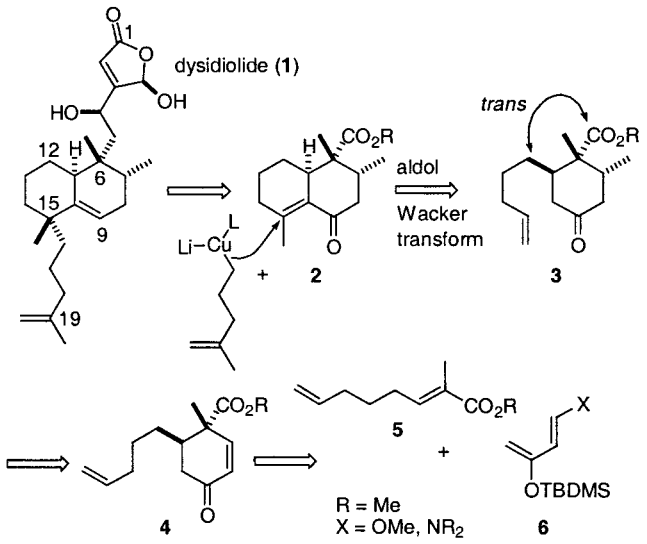
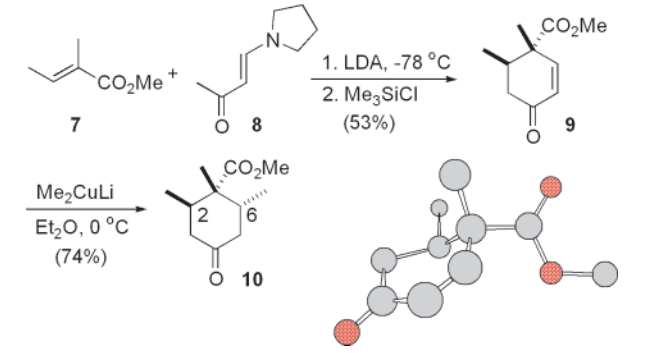


Figure 1. Retrosynthetic analysis for dysidiolide (**1**).

reaction. Since the ester group and the 4-pentenyl side chain are *trans*, preferentially the methyl group would be introduced through a cuprate addition, leaving the more stable *trans*-enoate **5** as a dienophile. Interestingly, the bicyclic enone **2** (R = Et) is also a key intermediate in a recently published synthesis of dysidiolide.[10] This prompted us to report our independent synthesis of the enone **2** (R = Me) which constitutes a formal total synthesis of dysidiolide (**1**).

Since the stereochemistry of the methyl cuprate addition to the enone **4** would be crucial to the success of our plan, we undertook a model study (Scheme 1). Knowing that

Scheme 1. Model Study for the Cyclohexanone Part; Chem3D Representation of the X-ray Structure of **9**

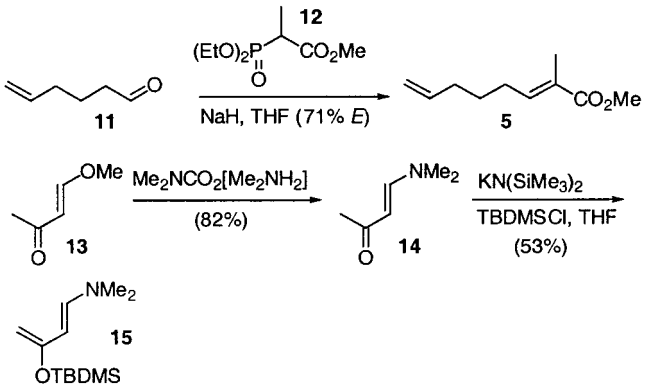


Diels–Alder reactions of 2,3-disubstituted acrylates are rather difficult, we considered the Rawal diene **6** (X = NR_2), which is more reactive than the Danishefsky diene **6** (X = OMe).[11–15] Alternatively, such cyclohexenones might be accessible by intermolecular double Michael addition between a vinylogous amide and an enoate.[16] Indeed, the cyclohexenone **9** could be directly prepared from the enolate of **8** by addition of methyl tiglate (1 equiv) at −78 °C (53%). Only one diastereomer was formed. Addition of trimethylsilyl chloride to the reaction mixture did not improve the yield, which indicates that the initial enolate reacts very fast with the vinylogous amide.[17] Alternatively, a cycloaddition reaction might be involved.

The structure of **9** was secured by an X-ray analysis. It shows that the ester group is in a pseudoequatorial position, the ring conformation being determined by the pseudoequatorial methyl group in the 6-position. Because of stereoelectronic reasons (chairlike transition state), we expected that the methyl cuprate would approach the enone *syn* to the ester group. This was indeed the case. Treatment of the enone **9** with dimethyl cuprate provided compound **10**, which is characterized by the appearance of two methyl doublets (δ = 0.88, 0.92) in the ^{1}H NMR spectrum. Because of symmetry considerations, this can only be the case if in ketone **10** the methyl groups in the 2- and 6-position are *trans* to each other. The stereochemical course of the addition is in contrast to a situation where the ester group is replaced by a 1,3-dithiane.[18]

With regard to the synthesis of the real system, we prepared the enoate **5** from the readily available 5-hexenal **11**.[19,20] A Wittig–Horner reaction between the phosphonate **12**[21] and the aldehyde **11** gave the desired *E*-isomer **5** (71%) together with a small amount (10%) of the *Z*-isomer, which could be separated by chromatography (Scheme 2). Unfortunately the direct condensation of enolate of **8** or **14** with enoate **5** was not satisfactory, in that it produced enone **4**

Scheme 2. Preparation of the Enoate **5** and the Diene **15**



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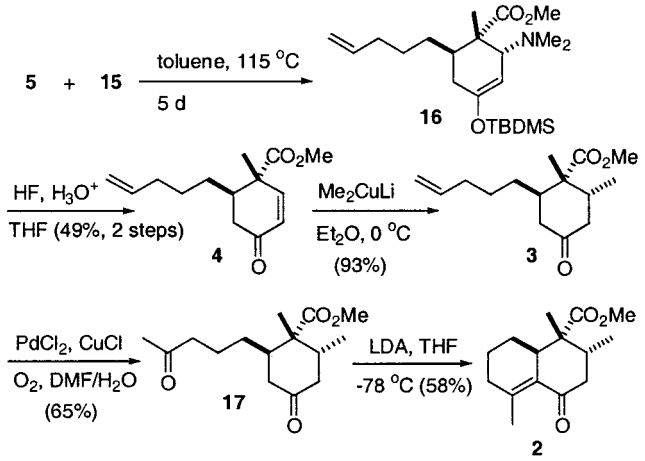
only in less than 10% yield. Therefore, the thermal Diels−Alder reaction of diene **15** with **5** was investigated. The precursor of **14**, the vinylogous amide, could be prepared in an efficient way from the vinylogous ester **13** by reacting it in dichloromethane at room temperature with the *N*,*N*-dimethylcarbamid acid dimethylammonium salt (Dimcarb) which is a convenient source of dimethylamine.[22,23] Silylation of **14** according to the literature gave the somewhat sensitive Rawal diene **15**.

It was found that the Diels−Alder reaction of **5** with **15** could be realized by heating the two components at 115 °C for 5 days (Scheme 3). Higher temperatures gave inferior

Scheme 3. Synthesis of the Enone **2**



yields. Usually, the cycloadduct **16** was not isolated but rather converted directly to the enone **4** by treatment with hydrogen fluoride (40% in H_2O). Continuing with the synthesis, a methyl group was introduced *trans* to the 4-pentenyl side chain by a stereospecific reaction with dimethyl cuprate, providing the ketone **3** in excellent yield. A subsequent Wacker oxidation[24−27] of **3** gave rise to the diketone **17**. The crucial intramolecular aldol condensation of **17** to the bicyclic enone **2** could be realized under basic conditions. Thus, addition of **17** to a THF solution of LDA followed by acidic workup furnished **2** in 58% yield. Alternatively, a potassium *tert*-butoxide induced cyclization was reported by Forsyth.[10] Since **2** has been converted to dysidiolide (**1**), the present work constitutes a formal total synthesis of this natural product.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds reported. In addition, copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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