Communications to the Editor

A Concise Total Synthesis of Dysidiolide through Application of a Dioxolenium-Mediated Diels−Alder Reaction

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A variety of structurally fascinating and biologically active natural products can be obtained from marine sources. The isolation, structural formulation, and biological evaluation of natural products from the aquatic biomass constitutes a frontier of growing importance in chemistry. In some instances, where the structures are especially novel or the biological profiles of action hold particular promise, a program in total synthesis may be appropriate. We felt that such a situation pertained in the case of dysidiolide (**1**), a sesterterpene isolated from the marine sponge *Dysidea etheria* de Laubenfels.[1] From a biogenetic point of view, structure **1** corresponds to a novel cyclization mode of an acyclic C_{25} isoprenoid precursor. Moreover, the difficultly available dysidiolide is a potent inhibitor of the human cdc25A protein phosphatase.[2,3] Since this class of enzymes (cdc25A, B and C) is involved in dephosphorylation of cyclin-dependent kinases, it has been proposed that inhibitors could produce specific cell cycle arrest. Early results have shown that dysidiolide inhibits growth of lung carcinoma and murine leukemia cell lines.[1]

We approached the total synthesis problem from the perspective of testing a dioxolenium (Gassman) type of activated dienophile (Figure 1).[4,5] We hoped to study a Diels−Alder reaction of the type **2** + **4**, wherein the presumed mechanistically active intermediate (**3**) would undergo cycloaddition in the regiosense indicated, and with tight diastereoface governance based on differing demands of R_1 and R_2. Most interesting was the matter of endo/exo selectivity. To reach **5**, it would be necessary for the dioxolenium function of **3** to direct endo in the Diels−Alder step.[4,5a,6] The realization of this line of thinking is described below in the context of a total synthesis of **1**.

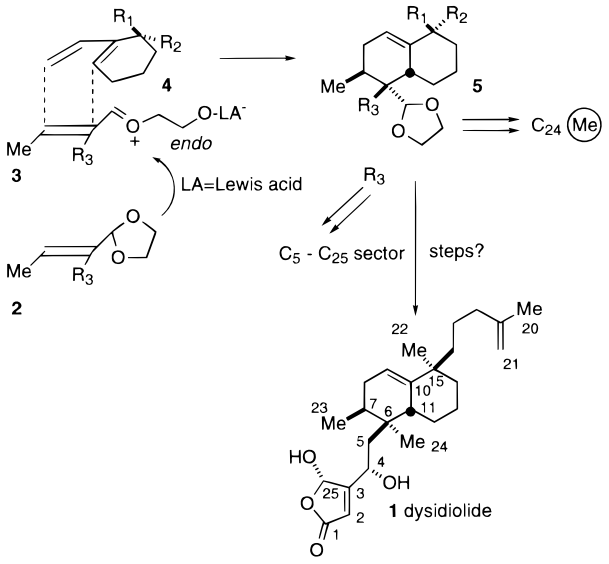
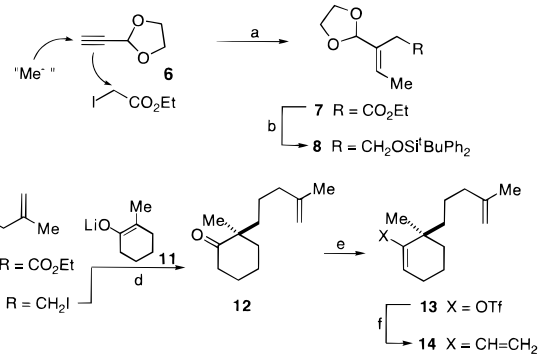


Figure 1.

Scheme 1[a]



[a] Reagents and conditions: (a) Me_2CuLi, Et_2O, −45 °C; ICH_2CO_2Et, HMPA, −55 °C to rt (30−55%). (b) Superhydride, THF, −78 to −20 °C; imidazole, TBDPSCl, −20 °C to rt (68%). (c) i. LAH, Et_2O; ii. TsCl, pyridine, 0 °C; iii. NaI, acetone, Δ (92% overall). (d) DME, HMPA, −55 °C to rt (49%). (e) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2 (87%). (f) CH_2═$CHSnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, Δ (80%).

The specific version of **2** which was selected to serve as the operative dienophile was acetal **8**. The synthesis of this compound was accomplished starting with known dioxolane **6** (Scheme 1).[7] Addition of lithium dimethylcuprate to **6**, followed by trapping with ethyl iodoacetate under the conditions indicated,[8] afforded olefin **7**. The ester function was converted to a protected two-carbon alcohol residue, as shown, to provide dienophile **8**.

The specific version of **4** selected as the operative diene was structure **14**. The synthesis of **14** commenced with the commercially available unsaturated ester **9**. The latter was converted

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(1) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759.

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(4) For examples of Diels−Alder reactions using allylic acetals as the dienophile, see: (a) Gassman, P. G.; Singleton, D. A.; Wilwerding, J. J.; Chavan, S. P. *J. Am. Chem. Soc.* **1987**, *109*, 2182. (b) Sammakia, T.; Berliner, M. A. *J. Org. Chem.* **1994**, *59*, 6890.

(5) For examples of Diels−Alder reactions using vinyl oxolenium ions derived from different dienophiles, see: (a) Gassman, P. G.; Chavan, S. P. *J. Org. Chem.* **1988**, *53*, 2392. (b) Gassman, P. G.; Chavan, S. P. *Tetrahedron Lett.* **1988**, *29*, 3407. (c) Gassman, P. G.; Chavan, S. P. *J. Chem. Soc., Chem. Commun.* **1989**, 837. (d) Hashimoto, Y.; Saigo, K.; Machida, S.; Hasegawa, M. *Tetrahedron Lett.* **1990**, *39*, 5625. (e) Hashimoto, Y.; Nagashima, T.; Hasegawa, M.; Saigo, K. *Chem. Lett.* **1992**, 1353. (f) Sipf, P.; Xu, W. *Tetrahedron* **1995**, *51*, 4551.

(6) For an example of a Diels−Alder reaction with a similar diene giving exo selectivity, see: Yoon, T.; Danishefsky, S. J.; de Gala, S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 85.

(7) (a) Giusti, G. *Bull. Chim. Soc. Fr.* **1972**, 753. (b) Le Coq, A.; Gorgues, A. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. 6, p 954.

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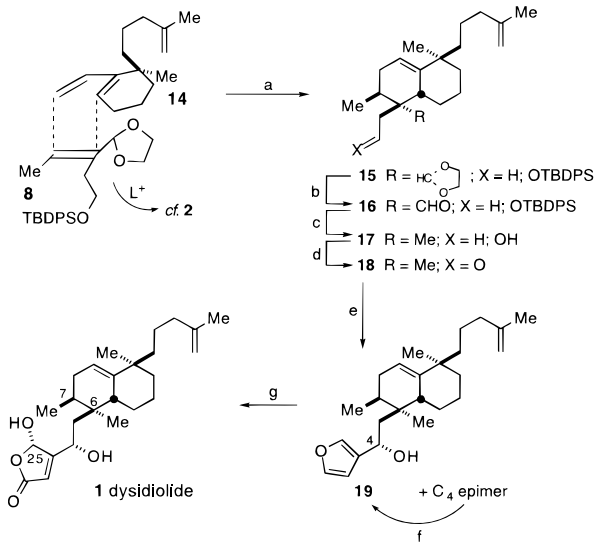
Scheme 2[a]



[a] Reagents and conditions: (a) TMSOTf, CH_2Cl_2, −90 °C (67%). (b) Montmorillonite K 10, CH_2Cl_2 (89%). (c) H_2NNH_2, KO^{t}Bu, *n*-butanol, sealed tube, 150 °C (74%). (d) TPAP, NMO, ms, CH_2Cl_2 (90%). (e) 3-Lithiofuran, THF, −78 °C (34% + 56% C4 epimer). (f) i. *p*-Nitrobenzoic acid, Ph_3P, DEAD, benzene; ii. DIBAL, CH_2Cl_2, 0 °C (81% overall). (g) O_2, Rose Bengal, DIPEA, CH_2Cl_2, *hν*, −78 °C (77%).

to known iodide **10** as described.[9] This compound served as an alklylating agent with respect to the lithium enolate of 2-methylcyclohexanone (**11**)[10] giving rise, albeit thus far in modest yield, to ketone **12**.[11] This substance was converted to vinyl triflate **13**[12] and then, by a Stille cross coupling,[13] to diene **14**.

Diels−Alder reaction between **8** and **14** was conducted under catalysis by TMSOTf[4b] as shown (Scheme 2). There was thus obtained a 67% yield of adduct **15**.[14] In addition, ca. 5% of a stereoisomer (structure not yet determined) was obtained. From adduct **15**, we advanced to dysidiolide in the manner shown. Cleavage of the ketal[15] in **15** was followed by Wolff−Kishner reduction of the aldehyde function in **16** to produce, upon concomitant desilylation, alcohol **17**. Following oxidation, aldehyde **18** was in hand. Addition of 3-lithiofuran[16] to this compound, under the conditions shown, gave rise to **19** and its C4 stereoisomer.[17] Photooxidation of **19** with singlet oxygen[16,18] provided a 77% yield of dysidiolide identical in all respects with the natural product by chromatographic and high-field NMR criteria.[1] As is the case with the natural product, dysidiolide, in solution, exists as a mixture of C_{25} diastereomers. Upon crystallization, this carbon emerges in the relative configuration shown.[1]

The power of the Gassman dioxolenium dienophile method is underscored by the fact that trisubstituted analogues of **8**, bearing ester dienophiles instead of the acetal, were ineffective in the Diels−Alder reaction. We also note that high selectivity for endo addition was observed when a dioxane acetal of (*Z*)-2-methyl-2-butenal was used as the dienophile in a Diels−Alder reaction with diene **14**. The adduct from this reaction was elaborated, leading to "dysidiolides" stereoisomeric with **1** at carbons 6 and 7. The synthesis and evaluation of these stereo analogues will be the subject of future disclosures.

With dysidiolide available to us through a concise total synthesis (albeit for the moment as the racemate), we have begun to investigate its biological profile. Indeed, within 24 h, dsyidiolide (2−50 μM) caused growth arrest on four human cancer cell lines. In PC3, TSU-Pr1, and DU145 prostate cancer cells, growth arrest was accompanied by massive apoptosis. In the MCF7 breast cancer cell line, the drug caused loss of the G_2/M peak and accumulation of cells in G_1. These data are consistent with the induction by dysidiolide of cell cycle specific growth arrest followed by apoptosis—a form of programmed cell death—in human cancer cells. At the chemical level, we are now attempting to obtain ketone **12**, or a functionally equivalent congener, in optically pure form, in a straightforward manner so as to pave the way for the synthesis of enantiomerically pure dysidiolide. Also, studies are currently in progress to ascertain the specificity of the biological target of dysidiolide and to pin down its effects on cell cycle progression and cytotoxicity in detail. Results in both areas will be described in due course.

Acknowledgment. We dedicate this paper to the memory of Professor Paul Gassman and to his many contributions to science. This work was supported by the National Institutes of Health [grant nos. HL25848 (S.J.D.) and P50CA68425-02, Breast Cancer Spore Grant (N.R.)]. S.R.M. gratefully acknowledges an NSERC (Canada) Postdoctoral Fellowship (188211). The authors thank Dr. Sarath Gunasekara of the Harbor Branch Oceanographic Institution for providing a sample of natural dysidiolide and Mr. Tony Hascall of Columbia University for his help in obtaining a key confirmatory X-ray crystal structure.[14] We are grateful to Vinka Parmakovich and Barbara Sporer of the Columbia University Mass Spectral Facility.

Note Added in Proof. Recently, the total synthesis of dysidiolide has been announced, see: Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425.

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(17) The undesired C4 epimer of **19** may be recycled, via oxidation to the ketone and subsequent reduction, to the desired stereoisomer. The reduction gives a mixture of C4 diastereomers that is processed. Alternatively, the undesired C4 epimer of **19** may be converted into the desired compound (81% yield) using a Mitsunobu inversion with *p*-nitrobenzoic acid and reduction of the resulting ester. See: Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
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