

Enantioselective Formal Total Synthesis
of (–)-Dysidiolide

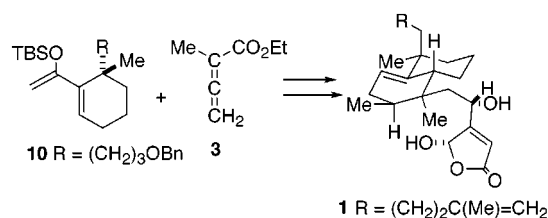
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ABSTRACT



An enantioselective formal total synthesis of the sesterterpene (–)-dysidiolide **1** beginning with an intermolecular Diels–Alder reaction of the allene ester **3** and the silyloxydiene **10** is reported.

Dysidiolide **1** was isolated from the Caribbean sponge *Dysidea etheria* de Laubenfels and claimed to be an inhibitor of protein phosphatase cdc25A with an IC₅₀ of 9.4 μM. It also inhibited the growth of the A-549 human lung carcinoma and P388 leukemia cell lines, with IC₅₀ values of 4.7 and 1.5 μM, respectively.¹ Because of its interesting sesterterpinoid structure with six stereocenters, it has attracted a large amount of synthetic interest which has culminated in several total or formal total syntheses.² A few analogues have also been prepared and tested for their inhibition of both cdc25A and tumor growth with contradictory results.³ One group^{3a} cited no activity for dysidiolide and its enantiomeric or racemic forms (IC₅₀ > 2000 μM) while the second^{3b} reported

good inhibition for the natural product and its close analogues (IC₅₀ 13–35 μM). We now report the enantioselective formal total synthesis of (–)-dysidiolide **1**, which begins with the intermolecular cycloaddition of an allene and a 2-silyloxydiene coupled with a novel stereoselective rearrangement of the [2 + 2] adduct to afford the normally less favorable exo Diels–Alder adduct, a process that we had described earlier.⁴

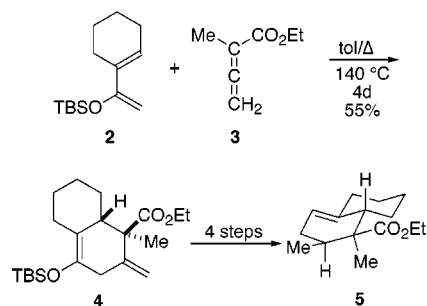
Recently we reported the cycloaddition of several 2-silyloxydienes, e.g., **2**, with the allenecarboxylate **3** which gave a mixture of exo and endo Diels–Alder adducts and the [2 + 2] cycloadduct (Scheme 1).⁴ This latter compound could be rearranged thermally by a highly diastereoselective process

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

(2) (a) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425. (b) Boukouvalas, J.; Cheng, Y. X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228. (c) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. *J. Am. Chem. Soc.* **1998**, *120*, 1615. (d) Brohm, D.; Waldmann, H. *Tetrahedron Lett.* **1998**, *39*, 3998. (e) Piers, E.; Caillé, S.; Chen, G. *Org. Lett.* **2000**, *2*, 2483. (f) Demeke, D.; Forsyth, C. *J. Org. Lett.* **2000**, *2*, 3177. (g) Miyaoka, H.; Kajiwara, Y.; Yamada, Y. *Tetrahedron Lett.* **2000**, *41*, 911. (h) Takahashi, M.; Dodo, K.; Hashimoto, Y.; Shirai, R. *Tetrahedron Lett.* **2000**, *41*, 2111. (i) Paczkowski, R.; Maichle-Mossmar, C.; Maier, M. E. *Org. Lett.* **2000**, *2*, 3967. (j) Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y. *J. Org. Chem.* **2001**, *66*, 1429.

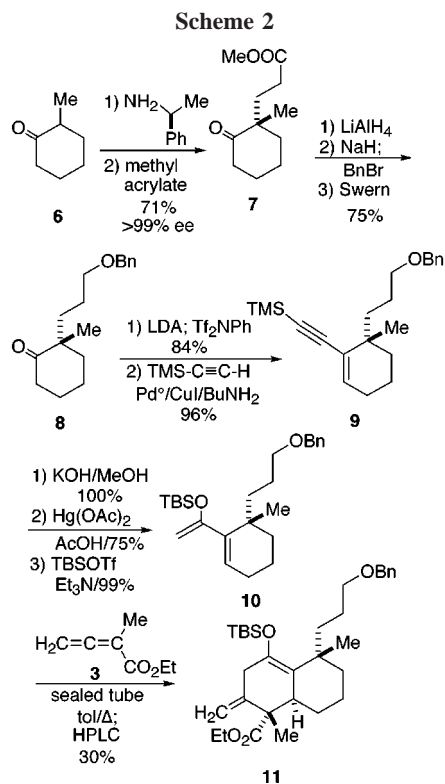
(3) (a) Blanchard, J. L.; Epstein, D. M.; Boisclair, M. D.; Rudolph, J.; Pal, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2537. (b) Takahashi, M.; Dodo, K.; Sugimoto, Y.; Aoyagi, Y.; Yamada, Y.; Hashimoto, Y.; Shirai, R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2571.

Scheme 1



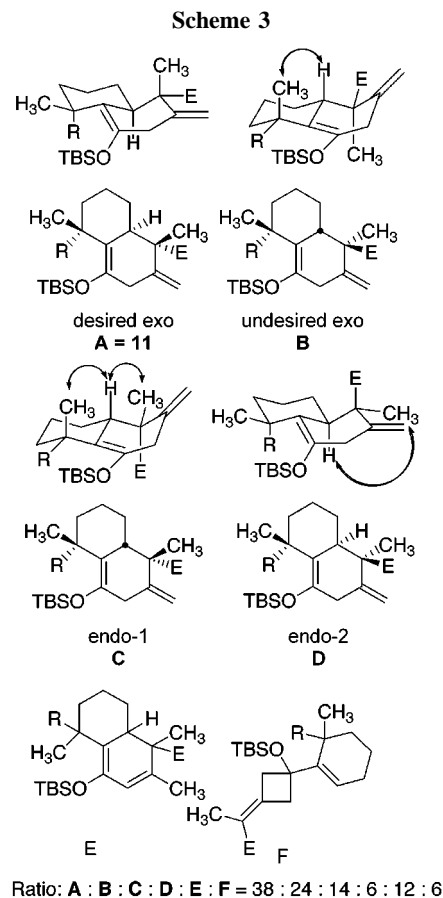
to give only the desired exo adduct so that one could isolate mainly the exo adduct, e.g., **4**, by heating for an extended period (e.g., 4 days). A four-step sequence (diastereoselective hydrogenation, desilylation, reduction, and highly regioselective dehydration) afforded the bicyclic ring system analogue of dysidiolide **5**. We now report the application of this route to the synthesis of the natural product itself.

Thus, racemic 2-methylcyclohexanone **6** was converted into the optically active keto ester **7** in 71% yield by the method of d'Angelo,⁵ which was first used in the dysidiolide area by Boukouvalas^{2b} (Scheme 2). The original ee of **7** of



86% was raised to >99% by recrystallization of the semicarbazone and hydrolysis. Reduction of both functional groups followed by selective protection of the primary alcohol and Swern oxidation afforded the keto benzyl ether **8** in 75% yield for the three steps (again by analogy to the work of Boukouvalas). Formation of the enol triflate (LDA, PhNTf₂, 84%) and Sonogashira coupling with (trimethylsilyl)acetylene furnished the enyne **9** in 96% yield. The alkyne produced by simple desilylation was hydrated under standard conditions to give in 75% yield the methyl ketone which was converted into the *tert*-butyldimethylsilyl (TBS) enol ether **10** with TBSOTf and triethylamine in 99% yield. Heating of **10** with the substituted allenecarboxylate **3** at 140 °C for 7 d gave, as expected, a mixture of several products, the major ones being the two exo Diels–Alder adducts in

which the dienophile had approached the diene from both directions, namely the desired face syn to the methyl group as well as the face anti to the methyl group. The mixture was separated by careful HPLC on a reverse phase column using acetonitrile as eluent to produce six distinct compounds (Scheme 3). These compounds were identified by extensive



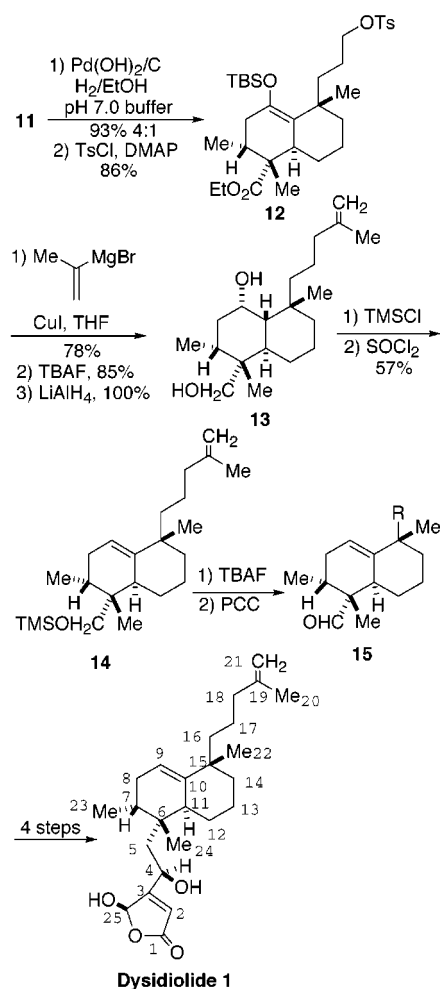
¹H NMR analysis including the use of HMBC and HMQC spectra and NOE experiments (shown with arrows in Scheme 3). As shown in Scheme 3, the desired exo isomer **A** (compound **11**) was the major isomer formed and could be isolated from HPLC in 30% yield from **10** and **3**. Interestingly, the second major isomer isolated is the opposite exo adduct **B** with the two endo adducts **C** and **D** being formed in 14% and 6% yield, respectively. It should be noted that it may be possible to convert the less favorable endo isomer **D** into the 4,6-bis-epimer of dysidiolide which has been shown to be more biologically active than dysidiolide **1** itself.^{3b} Finally small amounts of the [2 + 2] adduct **F** and the conjugated diene **E** were also isolated.

Conversion of **11** into the desired natural product dysidiolide followed our earlier route (Scheme 4). Thus, reduction of the exocyclic methylene was carried out as previously described⁴ but with the addition of a pH 7.0 buffer which was crucial to obtaining consistently high yields and good diastereoselectivity. Under these conditions one isolates a 4:1 mixture of the compound with the desired α -methyl

(4) Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, *121*, 3529.

(5) d'Angelo, J.; Desm ele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.

Scheme 4



group to the compound with the β -methyl group in 93% yield. This reduction step also removes the benzyl ether to give the primary alcohol which was converted into the tosylate **12** in 86% yield. Coupling of this tosylate with isopropenylmagnesium bromide in the presence of copper iodide gave the desired terpene side chain ($[\alpha]^{20}_D = -51.2^\circ$). Desilylation afforded the ketone with the *trans* ring junction (*trans*-decalin) ($[\alpha]^{20}_D = -34.5^\circ$) as we had shown in our earlier model study. Hydride reduction of both the ketone

and the ester gave the diol **13** ($[\alpha]^{20}_D = +0.7^\circ$). In this process, the normally favored axial attack on the cyclohexanone is disfavored due to 1,3-diaxial interaction of the methyl group with the incoming hydride and thus the hydride attacked the ketone from the normally disfavored equatorial direction to give the axial alcohol, as we had shown previously. Selective silylation of the primary neopentyl-like alcohol in the presence of the hindered axial secondary alcohol was accomplished using the method of Forsyth^{2f} to give the monoalcohol ($[\alpha]^{20}_D = -48.7^\circ$), which was eliminated using thionyl chloride in the presence of pyridine to give the desired trisubstituted alkene as expected on the basis of our earlier work.⁴ This furnished the diene silyl ether **14** which was identical by ¹H and ¹³C NMR⁶ with an authentic sample kindly provided by Demeke and Forsyth.^{2f} Desilylation of the silyl ether **14** with TBAF and oxidation of the alcohol afforded the aldehyde **15** which has been converted into dysidiolide **1** by the four-step sequence of homologation of the aldehyde (reaction with the methoxymethylene Wittig reagent and acidic hydrolysis followed by the well-known process (used often in the synthesis of dysidiolide) of addition of 3-lithiofuran and photooxidation). Thus, the preparation of **14** constitutes an enantioselective formal total synthesis of (-)-dysidiolide **1** from 2-methylcyclohexanone **6** via the key Diels–Alder addition of the silyoxydiene **10** and the allenecarboxylate **3**. Further work on the preparation of analogues of **1**, e.g., the 4,6-bis-epimer, is currently underway.

Acknowledgment. We thank the National Institutes of Health for financial support and Drs. Craig Forsyth and Damtew Demeke for a sample of an intermediate in their synthesis^{2f} which was identical to the keto ester (before the reduction to give **13**) of our synthesis, except for optical rotation.

Supporting Information Available: Spectral data and experimental procedures for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(6) The ¹³C NMR spectra of both **14** and the corresponding alcohol were essentially identical to those reported by Forsyth and Demeke.^{2f}