Total Synthesis of (+)-Dysidiolide

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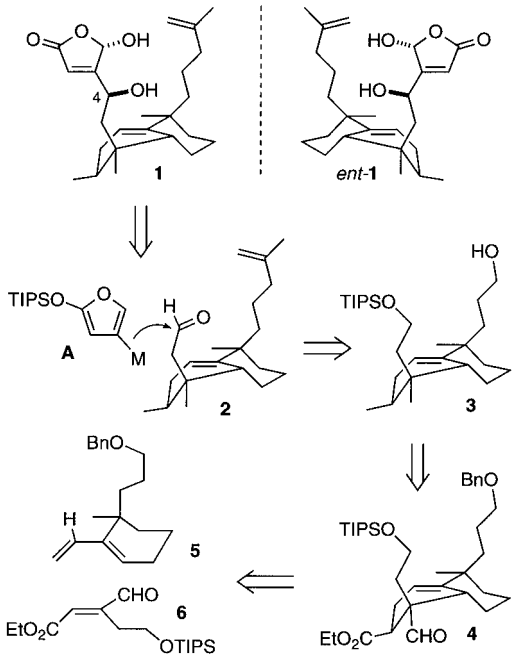
Dysidiolide (**1** or *ent*-**1**), a novel sesterterpenoid isolated in 1996 from the Caribbean sponge *Dysidea etheria* de Laubenfels, exhibits antitumor activity at the micromolar level, and most importantly, it is the first natural product discovered thus far to inhibit protein phosphatase cdc25A ($IC_{50} = 9.4\ \mu M$).[1] In addition to such remarkable biological properties, which may have utility in the treatment of cancer,[1,2] dysidiolide also possesses a unique carbon skeleton with structural features that find no precedent in nature. Central to the molecular array is the close proximity of the two side chains (ca. 4 Å apart) and the γ-hydroxylbutenolide residue, which is believed to serve as a surrogate phosphate when the molecule is bound to cdc25A.[1]

While the structure and relative stereochemistry of dysidiolide were determined by single-crystal X-ray analysis, its absolute configuration was not assigned.[1,3] We report here the first total synthesis of **1** that establishes the absolute stereostructure of natural dysidiolide as *ent*-**1** and provides the basis for producing a range of designed analogues for SAR studies.

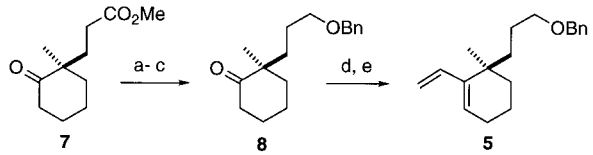
Our synthetic strategy (Scheme 1) entailed elaboration of **1** by addition of [(triisopropylsilyl)oxy]furan reagent **A** (M = Li or TiX_3) to aldehyde **2** and subsequent oxyfunctionalization of the furan ring by utilizing methodology developed in this laboratory.[4] The preferred conformer[5] of **2** (shown in Scheme 1) would undergo attack from the least hindered *re*-face of the carbonyl group, thereby setting the required *S*-stereochemistry at C-4. Convergent construction of the decalin framework was envisioned by Diels−Alder reaction of chiral diene **5** with the doubly activated dienophile **6**. Previous findings with similar dienophiles[6] suggested that both the regioselectivity and endo/exo selectivity should proceed as planned. Inspection of molecular models further suggested that the desired π-facial selectivity would be dictated by the preferred conformation of diene **5** (cf. Scheme 1), which minimizes $A^{1,2}$-strain.[7] Thus, all chirality in **1** would derive from the single stereocenter in **5**.

Diene **5** was prepared from methyl (*R*)-(+)-1-methyl-2-oxocyclohexanepropionate (**7**, ca. 90% ee)[8] by reduction to the corresponding diol,[9] selective benzylation of the primary alcohol, TPAP-oxidation,[10] addition of vinylcerium dichloride[11] and dehydration of the resulting allylic alcohol by heating in the presence of $CuSO_4$ (Scheme 2). The overall yield of this five-step sequence was 64.6%.[12]

Scheme 1



Scheme 2[a]



[a] Key: (a) $LiAlH_4$, THF, 65 °C, 100%; (b) NaH, THF, BnBr, 76%; (c) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 100%; (d) CH_2=CHMgBr, $CeCl_3$, THF, rt; (e) $CuSO_4$, PhH, 80 °C, 85% from **8**.

Access to dienophile **6** was gained in a fully stereoselective manner by ethoxycarbonylation of acetylene[13] **9**, conjugate addition of in situ generated lithium divinylcuprate,[14] and ozonolysis of the vinyl group[15] (Scheme 3).

With **5** and **6** in hand, we turned to the crucial Diels−Alder reaction, which proved especially serviceable under mediation by ethylaluminum dichloride in CH_2Cl_2 at −94 °C (Scheme 4). Under these conditions, only two of the eight possible adducts were produced (**4** and **12**) in a ratio of 2.3:1 (76% yield). Reduction of the so-obtained **4**/**12** mixture with $LiEt_3BH$ provided the easily separable diols[16] **13** and **14** in yields of 43 and 18%, respectively (over two steps).

In keeping with our plan, elaboration of diol **13** to intermediate **3** next required deoxygenation of the vicinal hydroxymethyl substituents (Scheme 5). This and the ensuing step, which entailed removal of the benzyl protecting

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(2) Millar, J. B. A.; Russell, P. *Cell* **1992**, *68*, 407.
(3) Structural elucidation by NMR was particularly difficult due to the presence of both lactol epimers in solution and/or the hindered motions of the lactol ring (ref 1).
(4) Boukouvalas, J.; Lachance. N. *Synlett* **1998**, in press.
(5) Molecular mechanics calculations using CHARMm forcefield quanta simulation software indicated that this conformer corresponds to the lowest energy minimum and is favored by at least 1.1 kcal/mol over those susceptible to undergo *si*-face attack. We thank Professor Josée Brisson for invaluable assistance.
(6) Corey, E. J.; Desai, M. C. *Tetrahedron Lett.* **1985**, *26*, 5747. Kakushima, M.; Espinosa, J.; Valenta, Z. *Can. J. Chem.* **1976**, *54*, 3304.
(7) Johnson, F. *Chem. Rev. (Washington, D.C.)* **1968**, *68*, 375.
(8) Ketone **7** and its antipode are commercially available or easily prepared on a large scale from racemic 2-methylcyclohexanone by d'Angelo's two-step procedure: d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.
(9) Tori, M.; Kosaka, K.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2039.
(10) Ley, S. V.; Norman J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(11) The use of freshly dried $CeCl_3$ was essential for optimal results; see also: Ladouceur, G.; Paquette, L. A. *Synthesis* **1992**, 185. Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787.
(12) Yields refer to chromatographically and spectroscopically homogeneous products. All new compounds exhibited satisfactory elemental analyses and/or exact mass data.
(13) Lipshutz, B. H.; Wood, M. R. *J. Am. Chem. Soc.* **1993**, *115*, 12625.
(14) Keck, G. A.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. Krause, N. *Tetrahedron Lett.* **1989**, *30*, 5219.
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(16) The structural assignments to these diols follow from NOE studies. Details of these experiments will be provided in the full paper.

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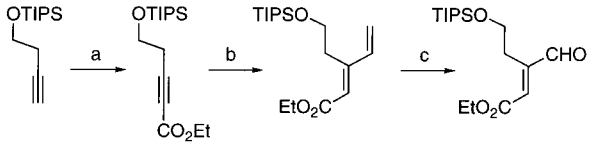
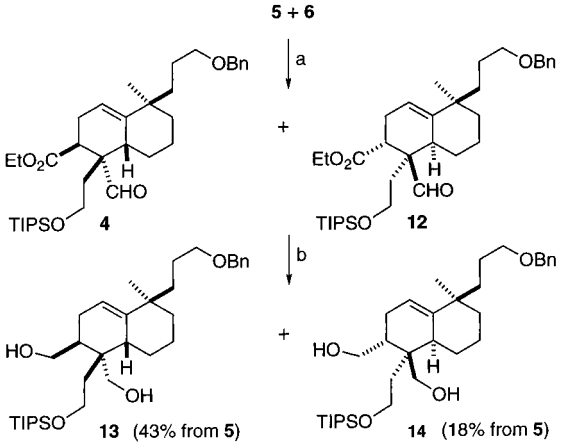
Scheme 3[a]



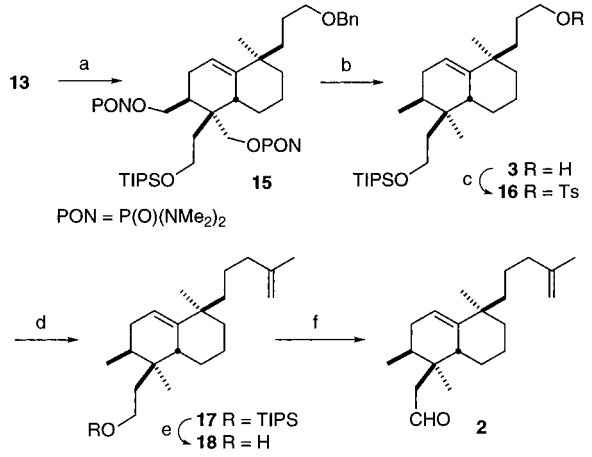
[a] Key: (a) EtMgBr, THF, then $ClCO_2Et$, −20 → 3 °C, 76%; (b) CH_2=CHLi, CuI, THF, −78 °C; (c) O_3, MeOH, CH_2Cl_2, −78 °C, then Me_2S, 70% from **10**.

Scheme 4[a]



[a] Key: (a) $EtAlCl_2$, CH_2Cl_2, −94 °C, 76%; (b) $LiEt_3BH$, THF, −78 °C.

Scheme 5[a]

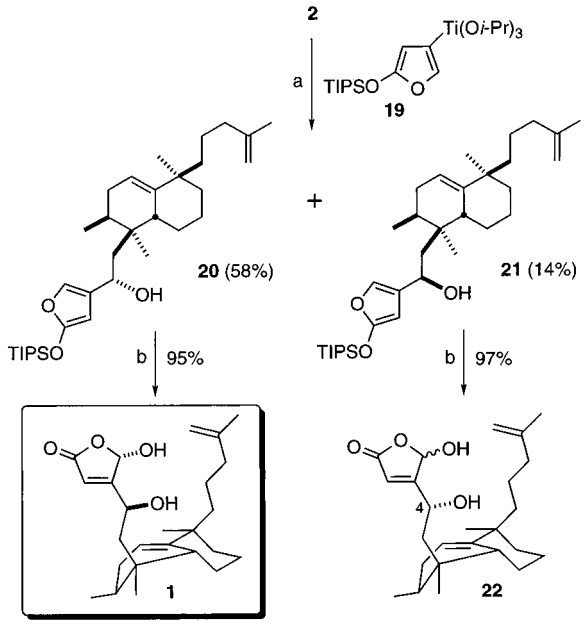


[a] Key: (a) MeLi, $(Me_2N)_2P(O)Cl$, DME, TMEDA (3:1), rt, 58%; (b) Li, $EtNH_2$, THF, *t*-BuOH, 0 °C, 70%; (c) TsCl, DMAP, CH_2Cl_2, 98%; (d) CH_2=C(CH_3)MgBr, CuI, THF, 0 °C, 91%; (e) TBAF, THF, 100%; (f) TPAP (4 mol %), NMO, 4 Å molecular sieves, 95%.

group, could be conveniently combined by adaptation of Ireland's phosphoramidate method.[17] Thus, conversion of **13** to diphosphoramidate **15** (58%) followed by Benkeser reduction ($Li/EtNH_2$) accomplished double deoxygenation along with debenzylation to furnish alcohol **3** in 70% yield. Tosylation of this alcohol followed by cross-coupling with isopropenylmagnesium bromide in the presence of freshly purified CuI, desilylation, and TPAP-oxidation[10] delivered aldehyde **2** with high efficiency (84.7%, four steps).

Exposure of **2** to ca. 4 equiv of (siloxyfuranyl)titanium reagent **19**[18] in ether at −78 °C provided the epimeric alcohols[19] **20** and **21** in 58 and 14% yields after purification by flash chromatography (Scheme 6). Sequential treatment[4] of the major isomer **20** with dimethyldioxirane in acetone

Scheme 6[a]



[a] Key: (a) **19**, −78 °C, Et_2O; (b) dimethyldioxirane (1.1 equiv), Me_2CO, −78 °C, 1 h, then Amberlyst-15, Me_2CO, H_2O, rt, 1.5 h.

(1 h, −78 °C) and Amberlyst-15/H_2O (1.5 h, rt) afforded (+)-dysidiolide (**1**) in 95% yield. Synthetic **1** so obtained was identical with an authentic sample of natural dysidiolide[20] by TLC, HPLC (co-injection, two solvent systems), IR, low- and high-resolution MS, and 500 MHz ^1H and 125 MHz ^{13}C NMR. The synthetic material had mp 181−184 °C and $[\alpha]^{22}_D$ +10.5° (*c* 0.5, MeOH/CH_2Cl_2, 1:1) as compared to mp 186−187 °C and $[\alpha]^{22}_D$ −11.1° (*c* 0.6, MeOH/CH_2Cl_2, 1:1) for the natural product.[1] These data establish that the absolute configuration of natural dysidiolide is as depicted in *ent*-**1** (Scheme 1). For the sake of comparison, we also converted alcohol **21** to (+)-4-*epi*-dysidiolide **22** (97%, Scheme 6). The latter was obtained as a colorless oil, $[\alpha]^{22}_D$ +65° (*c* 0.55, MeOH/CH_2Cl_2, 1:1), which could be further distinguished from **1** by ^1H and ^{13}C NMR and by HPLC.

In summary, we have achieved the first synthesis of (+)-dysidiolide (**1**), which allowed the absolute stereostructure of natural dysidiolide to be assigned as *ent*-**1**. The approach is convergent and efficient (longest linear route = 15 steps, overall yield 5.26%) and should be equally useful for making *ent*-**1** (from the antipode of **7**)[8] and a range of novel analogues for biological investigations.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds along with copies of 500 MHz ^1H NMR spectra of **1**, **22**, and natural dysidiolide (21 pages).

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(18) Reagent **19** was prepared from 4-bromo-2(5*H*)-furanone by silylation (TIPSOTf, Et_3N, CH_2Cl_2, 0 °C, 90%, cf. ref 4), bromine−lithium exchange (1.2 equiv of *n*-BuLi in Et_2O, −78 °C) and transmetalation (ClTi(O-*i*-Pr)$_3$, −78 to +25 °C) using Eberbach's procedure (Haarmann, H.; Eberbach, W. *Tetrahedron Lett.* **1991**, *32*, 903).

(19) Alcohols **20** and **21** were produced in excellent yield (>90%) and a ratio of 2.2:1, as determined by HPLC analysis of the crude reaction mixture. The relatively low yield of the minor isomer **21** after chromatography, which was less polar than **20**, was due to partial coelution with the 2-[(triisopropylsilyl)oxy]furan byproduct arising by hydrolysis of unreacted **19**.

(20) We are grateful to Dr. Sarath Gunasekera of Harbor Branch Oceanographic Institution for a sample of natural dysidiolide.