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A Formal Total Synthesis of the Sesterterpenoid (±)-Dysidiolide and Approaches to the Syntheses of (±)-6-Epi-, (±)-15-Epi-, and (±)-6,15-Bisepidysidiolide

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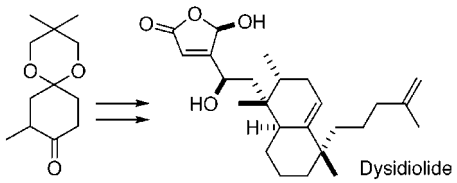
ABSTRACT



A formal total synthesis of the sesterterpenoid (±)-dysidiolide (1), a structurally novel sponge metabolite that inhibits the cdc25A protein phosphatase, and approaches to the syntheses of (±)-15-epi- (34), (±)-6-epi- (36), and (±)-6,15-bisepidysidiolide (39) are described.

In 1996, Gunasekera, Clardy, and their co-workers reported[1] the isolation of (−)-dysidiolide from the marine sponge *Dysidea etheria* de Laubenfels. It was shown[1] by an X-ray crystallographic study that this natural product is a constitutionally unusual sesterterpenoid and that it possesses the *relative* configuration indicated in structural formula **1** (Figure 1).[2] Interestingly, the X-ray investigation showed that, in the crystalline form, dysidiolide exists in a conformation in which both of the "floppy" side chains at C-6 and C-15 are axially (or pseudoaxially) oriented (see Figure 1). It was also established[1] that **1** is a cdc25A protein phosphatase inhibitor and, consequently, that this substance "may have utility in the treatment of cancer and other proliferative disorders."

Because of its atypical structure and its potentially important physiological activity,[1] dysidiolide has attracted considerable attention as a target for total synthesis.[3−7] The first reported total synthesis,[3] as well as that described in a very recent report,[7] produced (−)-dysidiolide and thus established that the natural product has the *absolute* configuration displayed in **1**. Boukouvalas et al.[5] constructed (+)-dysidiolide (the enantiomer of **1**), while two groups[4,6] have described syntheses of the racemic version of **1**. Interestingly,

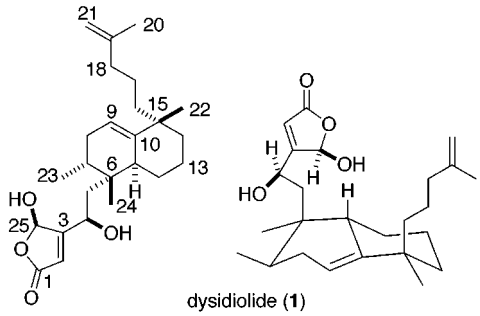


Figure 1.

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

(2) The numbering system shown in structural formula **1** is that proposed in ref 1.

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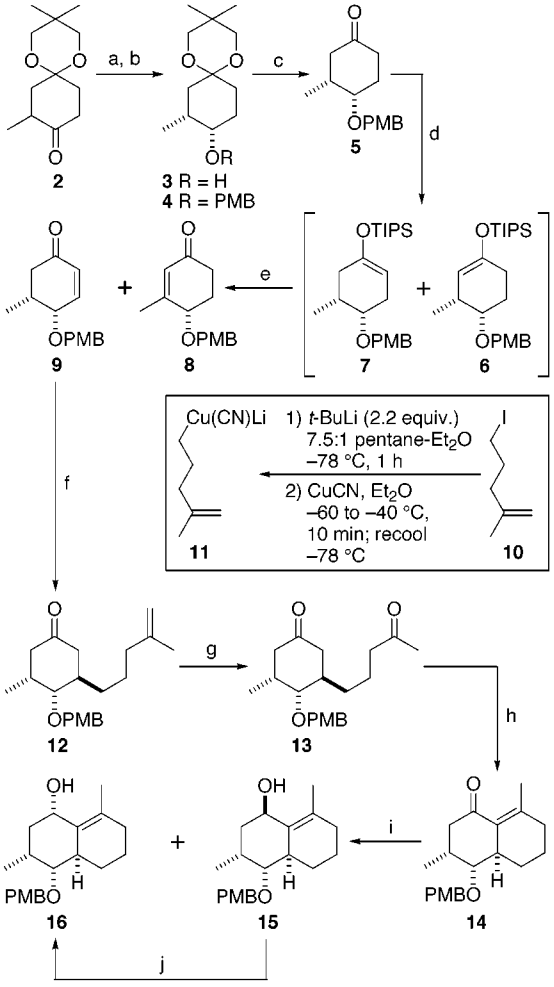
four of the five reported syntheses employed Diels−Alder reactions (either inter-[4,5,7] or intramolecular[6]) as key transformations in the overall synthetic pathways. On the other hand, the synthesis reported by Corey and Roberts[3] involved the transformation of a known, enantiomerically pure bicyclic ketal enone into the target substance. We report herein an alternative synthesis of (±)-dysidiolide (**1**) via an approach quite different from those described previously.

The initial portion of the synthesis, involving conversion of the known ketone **2**[8] into the bicyclic alcohol **16**, is summarized in Scheme 1. Reduction of **2** with lithium tri-*sec*-butylborohydride (L-Selectride)[9] provided, highly stereoselectively, alcohol **3**,[10] which was readily transformed, via the corresponding *p*-methoxybenzyl (PMB) ether **4**, into cyclohexanone **5** (73% from **2**). Sequential treatment of **5** with potassium hexamethyldisilazide (KHMDS) and triisopropylsilyl triflate (TIPS-OTf) gave, in essentially quantitative yield, a mixture of the positional isomers **6** and **7**, in a ratio of ∼1:3.3, respectively. Reaction of this mixture with iodosobenzene−trimethylsilyl azide in dichloromethane,[11] followed by treatment of the resultant *β*-azido TIPS enol ether intermediates with tributylammonium fluoride (TBAF) in THF,[11] furnished a mixture of enones **8** and **9**. Chromatographic separation of these materials gave the required isomer **9** in 59% yield from **5**.

Scheme 1[a]



[a] Reagents and conditions: (a) L-Selectride, THF, −78 °C, 2 h; H_2O_2, NaOH, H_2O, rt, 16 h (99%); (b) NaH, DMF, 0 °C; Bu_4NI (catalytic amount), PMB-Cl, 0 to 50 °C, 3 h; (c) conc hydrochloric acid, acetone, rt, 30 min (74% from **3**); (d) KHMDS, THF, −78 °C, 1 h; TIPS-OTf, Et_3N, THF, −78 °C, 1 h (99%; **6**:**7** ∼1:3.3) (e) PhIO, TMS-N_3, CH_2Cl_2, −25 to −18 °C, 15 min; TBAF, THF, −10 °C, 10 min (**8**: 20% from **5**; **9**: 59% from **5**); (f) reagent **11** (3.0 equiv), TMS-Br, pentane−Et_2O, −78 °C, 2 h; NH_3, NH_4Cl, H_2O (pH 8); TBAF, Et_2O, rt, 1 h (84%); (g) O_3, solvent red 23, 2:1 CH_2Cl_2−MeOH, −78 °C; Me_2S (75%); (h) NaOH, MeOH, reflux, 48 h (77%); (i) DIBALH, THF, −98 °C, 1 h; solid Na_2SO_4·$10H_2O$ (**15**: 46%; **16**: 47%); (j) Ph_3P, DEAD, $PhCO_2H$, THF, 0 °C to rt, 6 h; $LiAlH_4$, Et_2O, 0 °C (72%).

Cuprate reagent **11** required for conversion of enone **9** into functionalized cyclohexanone **12** was prepared as shown in Scheme 1. Thus, treatment of iodide **10** with *t*-BuLi at low temperature effected lithium−iodine exchange and the resultant lithio reagent, upon reaction with copper(I) cyanide, gave a solution of **11**. Reaction of this reagent with enone **9** in the presence of trimethylsilyl bromide (TMS-Br),[12] followed by brief treatment of the crude product with TBAF, provided **12** in 84% yield. Ozonolytic cleavage[13] of the alkenic bond of **12** provided dione **13**, which, upon treatment with NaOH in refluxing methanol, was transformed into bicyclic enone **14** (58% from **12**). Reduction (DIBALH) of **14** afforded a 1:1, chromatographically separable mixture of diastereomeric alcohols **15** and **16**. The unwanted isomer **15** was subjected to the Mitsunobu reaction (triphenylphosphine, diethyl azodicarboxylate (DEAD), benzoic acid),[14] and the acquired benzoate was reduced ($LiAlH_4$) to give an additional quantity of **16**. The overall yield of **16** from **14** was 80%.

Conversion of allylic alcohol **16** into the highly functionalized bicyclic aldehyde **32** is outlined in Scheme 2. Subjection of **16** to the Eschenmoser−Claisen rearrangement[15] provided an excellent yield of dimethylamide **17**, which, upon reduction with lithium triethylborohydride (Super-Hydride),[16] gave primary alcohol **18** (87% from **16**). The corresponding aldehyde **19** was produced cleanly and

(3) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425.
(4) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1615.
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(9) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
(10) All new compounds reported herein that were isolated and purified exhibited spectra in accord with assigned structures and gave satisfactory elemental (C, H) combustion analyses and molecular mass determinations (high-resolution mass spectrometry). Substances **26** and **27** were fully characterized as epimeric mixtures. Each of the intermediates **6**, **7**, **22**, and **30** was used for the next transformation without rigorous purification and was not fully characterized.
(11) Magnus, P.; Evans, A.; Lacour, J. *Tetrahedron Lett.* **1992**, *33*, 2933.
(12) Piers, E.; Oballa, R. M.; *J. Org. Chem.* **1996**, *61*, 8439.
(13) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.
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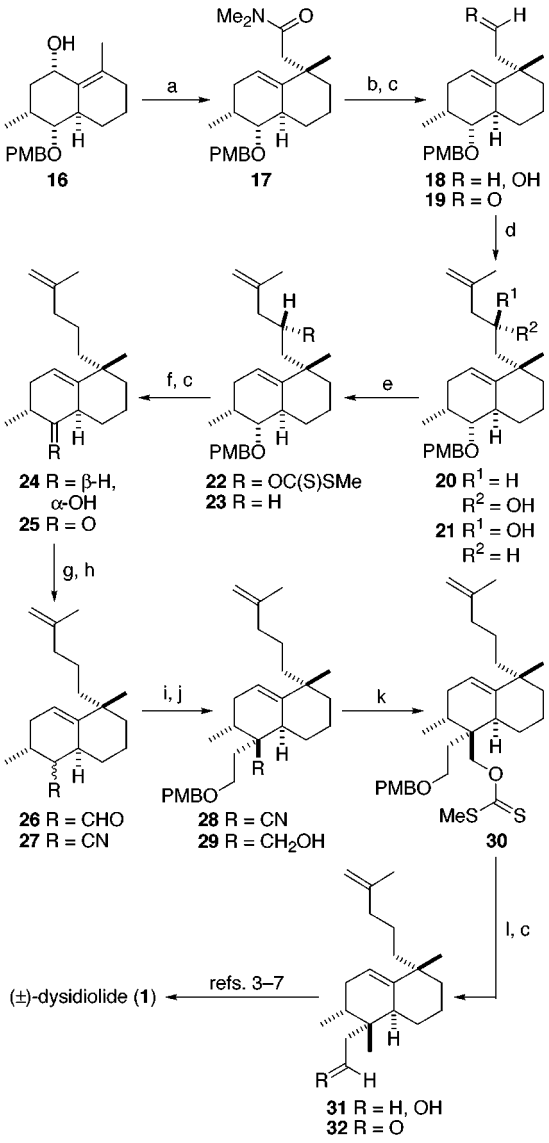
Scheme 2[a]



[a] Reagents and conditions: (a) $Me_2N-C(OMe)_2Me$, PhMe, 100 °C, 4 h (93%); (b) $LiEt_3BH$, THF, rt; H_2O_2, NaOH, H_2O, 50 °C, 2 h (94%); (c) Dess−Martin periodinane, CH_2Cl_2, rt (99%); (d) methallyl bromide, indium metal, DMF, rt, 2 h (**20**: 83%; **21**: 15%); (e) BuLi, THF, rt, 10 min; CS_2, rt, 1 h; MeI, rt, 30 min (96%); Bu_3SnH, AIBN, PhMe, reflux, 15 min (82%); (f) DDQ, 18:1 $CH_2Cl_2-H_2O$, rt, 1 h (97%); (g) $[Me_3Si(MeO)CH]Li$, THF, −35 °C, 1 h; NH_4Cl, H_2O; 1:1:8 $CF_3CO_2H-H_2O-CHCl_3$, 0 °C, 1 h (88%); (h) $(HO-NH_3)Cl$, NMP, 75 °C, 30 min; 115 °C, 3 h (96%); (i) KDA, THF, −78 °C, 30 min; $PMBO-CH_2CH_2-I$, HMPA, −78 °C, 10 min (88%); (j) DIBALH, DME, rt, 1 h; citric acid, H_2O, 3 h; $NaBH_4$, MeOH, rt, 20 min (79%); (k) NaH, imidazole (catalytic amount), THF, 60 °C, 2 h; CS_2, rt, 1h; MeI, rt, 30 min (99%); (l) Ph_2SiH_2, benzoyl peroxide, *o*-xylene, 150 °C, 40 min; DDQ, 18:1 $CH_2Cl_2-H_2O$, rt, 1 h (81%).

quantitatively by oxidation of **18** with the Dess−Martin reagent.[17] Treatment of **19** with methallyl bromide and indium metal in DMF,[18] followed by chromatographic separation of the resultant diastereomeric mixture on silica gel, provided alcohols **20** and **21** in yields of 83 and 15%, respectively. It turned out that minor isomer **21**, upon recrystallization from heptane, provided crystals (mp 90−92 °C) suitable for an X-ray crystallographic study.[19] By this means, the relative configurations of **20** and **21**, as well as those of previous intermediates in the synthetic sequence, were conclusively established.

Sequential treatment of a THF solution of **20** with butyllithium, carbon disulfide, and iodomethane provided xanthate **22**, which, upon reaction with tributylstannane and 2,2′-azobis(isobutyronitrile) (AIBN)[20] in refluxing toluene, afforded the functionalized bicycle **23** (79% from **20**). In a similar fashion, minor alcohol **21** was transformed into **23** in 77% yield. Cleavage[21] of the PMB ether function of **23** and Dess−Martin oxidation[17] of the acquired alcohol **24** gave ketone **25** in 89% overall yield. Homologation of ketone **25** was carried out by use of the Magnus−Roy protocol.[22] Thus, reaction of **25** with (methoxy(trimethylsilyl)methyl)lithium in THF at low temperature, followed by treatment of the resultant tertiary alcohol with aqueous trifluoroacetic acid in chloroform, provided aldehyde **26** (mixture of diastereomers) in 88% yield. Conversion of **26** into the corresponding mixture of nitriles **27** was effected in 96% yield by treatment of the former substance with hydroxylamine hydrochloride in *N*-methylpyrrolidinone (NMP) at 75−115 °C.[23]

Alkylation of the mixture of nitriles **27** proved to be efficient and highly stereoselective. Treatment of **27** with potassium diisopropylamide (KDA)[24] and 1-(*p*-methoxybenzyloxy)-2-iodoethane in THF at −78 °C provided a single alkylated product **28** in 88% yield. Reduction of the latter substance with DIBALH in DME, followed by immediate treatment of the resultant aldehyde with sodium borohydride in MeOH, produced primary alcohol **29**, which was readily converted[25] into xanthate **30** (99% yield). Treatment of **30** with diphenylsilane and benzoyl peroxide in *o*-xylene at 150 °C,[26] and reaction of the resultant mixture[27] with DDQ,[21] provided alcohol **31** in 81% yield. Dess−Martin oxidation[17] of **31** gave aldehyde **32** (95%). The ^1H and ^{13}C NMR spectral data derived from the latter material[28] agree very well with those reported by Corey and Roberts[3] and Boukouvalas et al.,[5] respectively. Since **32** was previously converted into

(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.
(18) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.

(19) This study was carried out by Dr. Brian Patrick, Manager, UBC X-ray Crystal Structure Laboratory. Details will be reported elsewhere.
(20) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
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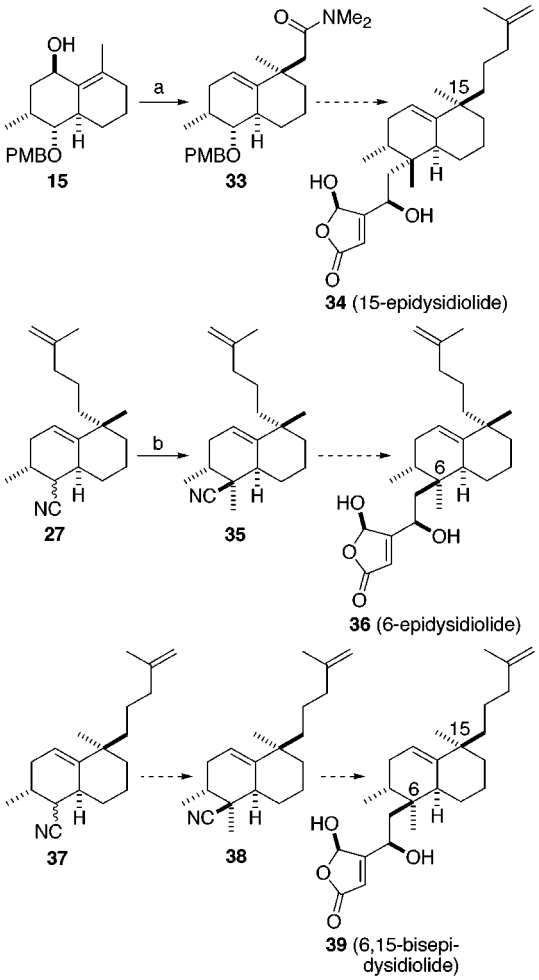
(25) Huffman, J. W.; Raveendranath, P. C. *J. Org. Chem.* **1986**, *51*, 2148.
(26) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. S. *Tetrahedron* **1991**, *46*, 8969.
(27) The radical deoxygenation step (ref 26) caused partial cleavage of the PMB ether function to give a mixture of **31** and its PMB ether.
(28) Compound **32** (colorless oil): ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (t, 1 H, J = 3.2 Hz), 5.33 (m, 1 H), 4.67 (s, 1 H), 4.64 (s, 1 H), 2.33 (dd, 1 H, J = 14.4, 2.8 Hz), 2.24 (dd, 1 H, J = 14.4, 3.6 Hz), 2.09−1.90 (m, 4 H), 1.82−1.76 (m, 1 H), 1.68 (s, 3 H) 1.74−1.50 (m, 6 H), 1.35−1.08 (m, 5 H), 1.07 (s, 3 H), 0.99 (s, 3 H), 0.84 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 204.4, 146.2, 145.0, 117.1, 109.7, 47.1, 42.4, 42.0, 40.0, 38.6, 37.6, 37.0, 33.0, 31.6, 29.3, 26.0, 23.0, 22.5, 22.4, 22.3, 14.9.

Scheme 3[a]



[a] Reagents and conditions: (a) $Me_2N-C(OMe)_2Me$, PhMe, 100 °C, 3 h (86%); (b) LDA, THF, HMPA, 0 °C, 45 min; MeI, −78 °C, 10 min (84%).

dysidiolide,[3−7] acquisition of this material completes a formal total synthesis of (±)-**1**.

It has been suggested[1] that dysidiolide's binding to the cdc25A protein phosphatase, along with its resultant biological activity, may be related to the fact that, structurally, the two floppy side chains at C-15 and C-6 of **1** project in a parallel fashion from one side of the overall plane of the bicyclic core of the natural product (see Figure 1). Consequently, to determine what effect changes in the configurations at C-15 and C-6 would have on biological activity, it would be of some interest to synthesize the diasteromeric substances 15-epi- (**34**), 6-epi- (**36**), and 6,15-bisepidisydiolide (**39**) (Scheme 3). The overall strategy employed in the synthetic work summarized in Schemes 1 and 2 would appear to be ideally suited for such an endeavor. Indeed, subjection of alcohol **15** to the Eschenmoser−Claisen rearrangement protocol[15] provided, in 86% yield, amide **33** (Scheme 3). The latter substance, which is epimeric with the previously prepared compound **17** (Scheme 2), would undoubtedly serve as a precursor for the construction of 15-epidisydiolide (**34**). On the other hand, methylation (LDA, THF, HMPA; MeI) of nitrile **27** afforded, in 84% yield, the single product **35**, which should function as a suitable intermediate for the synthesis of 6-epidysidiolide (**36**). Finally, methylation of the nitrile **37** (derivable from **33** via a pathway similar to that outlined in Scheme 2 for the transformation **17** → **27**) should give **38**. It is highly likely that the latter nitrile could be transformed into 6,15-bisepidysidiolide (**39**). The results derived from these ongoing investigations will be reported in detail in due course.

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