ORGANIC LETTERS

2000
Vol. 2, No. 20
3177−3179

Novel Total Synthesis of the Anticancer Natural Product Dysidiolide

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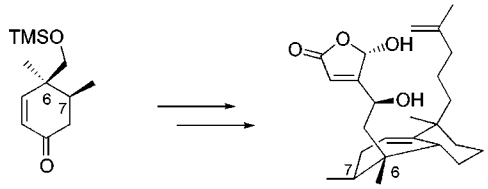
Received July 24, 2000

ABSTRACT



Dysidiolide (**1**)

The marine natural product dysidiolide has been synthesized in a highly diastereoselective fashion that features the sequential transfer of chirality from a cyclohexenone precursor.

Dysidiolide (**1**), a sesterterpene γ-hydroxybutenolide isolated from the marine sponge *Dysidea etheria* de Laubenfels, is a structurally unique compound with distinct biological properties.[1] The natural product is an unusual bicyclic C_{25} isoprenoid with an array of stereocenters including two quaternary centers and two axially disposed appendages in close spatial proximity (~4 Å). Interestingly, (−)-**1** had originally been reported to be a potent inhibitor of the human cdc25A protein phosphatase,[1] a potential target for anticancer therapy, and to inhibit the growth of A-549 human lung carcinoma and P388 murine leukemia cell lines at low micromolar concentrations. Corroboration of the dramatic anticancer activity has been provided with racemic **1**,[2] although the in vitro activity of the cdc25A catalytic domain toward the natural substrate, phosphorylated Cdk2/cycA, was recently reported to be insensitive toward **1**.[3] Hence, the mode of anticancer activity of (−)-**1** remains unknown.

The biomedical potential and architectural novelty of **1** have made it an attractive synthetic target, with several total syntheses[4−6] and synthetic studies[7−10] reported to date. Whereas the first synthesis[4] elaborated a Wieland−Miescher ketone analogue, others have employed variations on a Diels−Alder theme to construct the bicyclic system. Herein, we present a conceptually novel total synthesis of dysidiolide characterized by a highly diastereoselective sequential transfer of chirality to install the core stereocenters. This work will support further studies aimed at fully understanding the breadth and causes of dysidiolide's anticancer activity.

In designing the synthesis of **1**, we recognized an opportunity for a diastereoselective generation of all of the stereocenters on the decalin core relative to the stereocenter at C7 of the natural product (Scheme 1, carbon numbering corresponds to that of **1**). Thus, the quaternary center at C6 would be installed by alkylation *anti* to the methyl group at C7 using the known keto-ester **2**.[11] After reductive carbonyl

(1) Gunaskera, G. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759−8760. These researchers reported that **1** inhibited the *p*-nitrophenolphosphate dephosphorylation activity of cdc25A at 9.4 μM.

(2) Magnuson, S. R.; Sepp-Lorenzo, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1615−1616.

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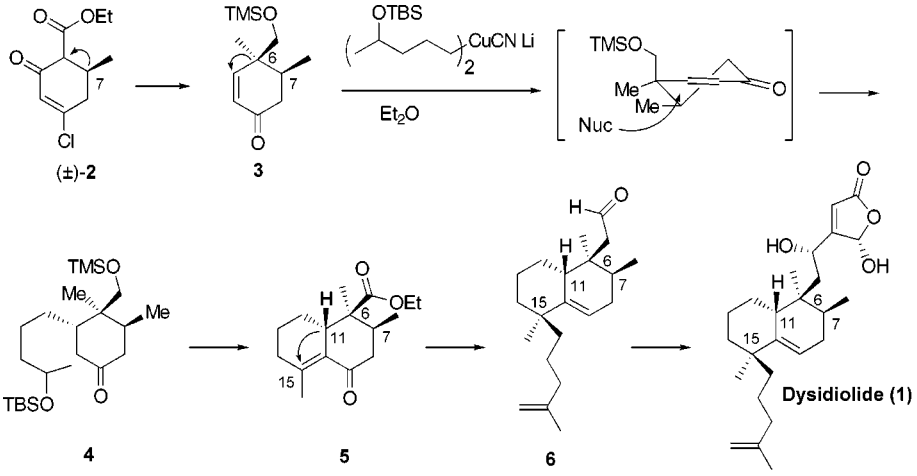
10.1021/ol006376z CCC: $19.00
Published on Web 09/14/2000

Scheme 1. Synthetic Plan for Dysidiolide via Sequential Transfer of Chirality



transposition to obtain the enone **3**, the stereocenter at the C11 ring juncture would be set by an axial conjugate addition of an annulation precursor, using the equatorial disposition of the vicinal methyl groups to lock the conformation of the enone and the shielding effect of the trimethylsilyl group to enhance diastereoselectivity. Following the transformation of the Michael adduct **4** to the enone **5**, the final quaternary stereocenter at C15 was to be installed by a conjugate addition of the pentenyl side chain on one diastereoface of the rigid bicyclic enone. Hence, all of the core stereocenters would be secured by a concise sequential transfer of chirality, taking full advantage of the conformations of key synthetic intermediates. Thereafter, convergence with the known aldehyde **6** would allow transformation to dysidiolide under previously reported conditions. Detailed below is the realization of this synthetic strategy.

The enone **5** proved to be an easily accessible intermediate. Its precursor, enone **3**, was prepared from the known keto-ester **2**[11] by the following sequence of reactions: alkylation with methyl iodide, vinylogous ester formation by treatment with sodium ethoxide, and reduction with lithium aluminum hydride followed by acid catalyzed rearrangement (Scheme 2). After protection of the primary alcohol as the trimethylsilyl ether, treatment with the higher order cyanocuprate prepared from the known bromide **7**[12] effected conjugate addition *anti* to the trimethylsilyloxy-methyl group of **3**. Simultaneous acid-catalyzed removal of both silyl protecting groups and subsequent oxidation using the Jones reagent provided a keto-acid, which was transformed to the keto-ester **9** upon treatment with potassium carbonate and ethyl iodide. Finally, annulation was accomplished by treatment with potassium *tert*-butoxide in ethanol to provide the desired bicyclic enone **5**. The synthesis of the decalin core of dysidiolide was completed by installation of the final ring stereocenter with a completely diastereoselective conjugate addition. The energy-minimized conformation of **5** depicted in Figure 1 indicates that the enone system is distorted from planarity by ~46°. Despite this diminished conjugation and the steric hindrance of the β,β-disubstituted bicyclic enone **5**, treatment with the Gilman reagent prepared from the bromide **10**,[13] and tributylphosphine followed by $BF_3{\cdot}OEt_2$ produced exclusively the 1,4-adduct in high yield.[14] The resulting keto-ester was reduced to the diol with lithium aluminum hydride, and the primary alcohol was selectively converted to the trimethylsilyl ether. Dehydration of the secondary alcohol with thionyl chloride provided the trisubstituted alkene **11**.

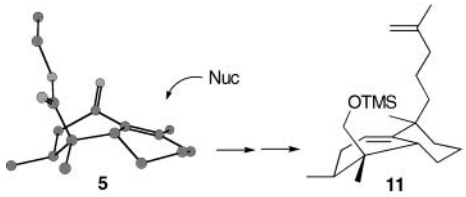


Figure 1. Energy-minimized conformation of distorted enone **5** supporting the diasterofacial selectivity of conjugate addition.

To converge with the target aldehyde **6**, homologation of the carbinol chain by one carbon was required. To this end, the trimethylsilyl protecting group of **11** was removed and the resulting primary alcohol was oxidized to an aldehyde. Treatment of the aldehyde with methoxymethyltriphenylphosphonium ylide followed by treatment of the resulting vinyl

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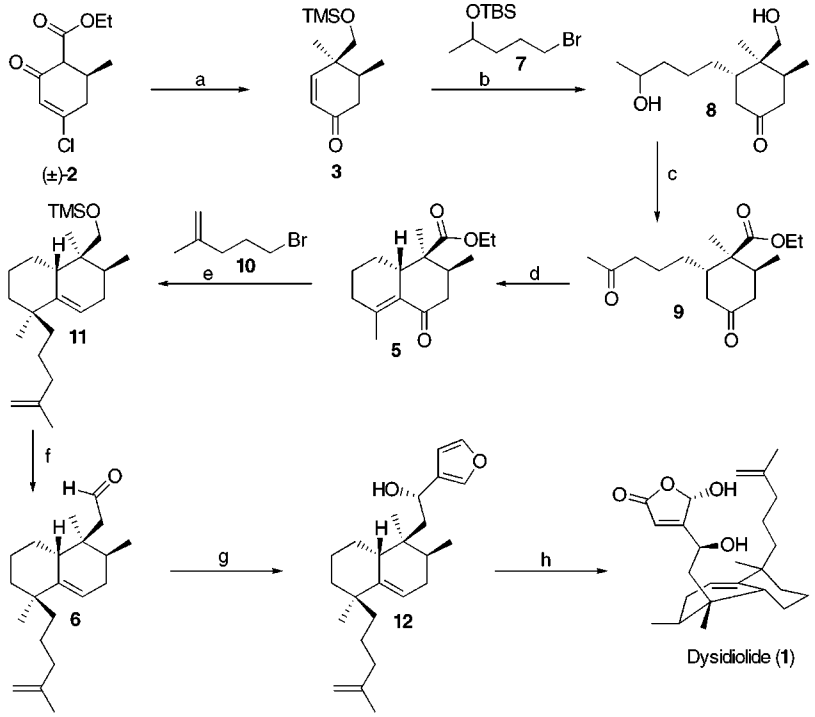
(13) Gen, A.; Wiedhaup, K.; Swoboda, J. J.; Dunathan, H. C.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 2656−2672.

(14) Attempted conjugate additions to enone **5** of alkylcopper(I)−BF_3 species (Yamamoto, Y.; Yamamoto, S., Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119) with (Oppolzer, W.; Moretti, R.; Godel, T.; Meuner, A.; Löher, H. *Tetrahedron Lett.* **1983**, *24*, 4971) or without phosphine, or cuprates with (Smith, A. B., III; Jerris, P. J. *J. Org. Chem.* **1982**, *47*, 1845) or without $BF_3{\cdot}OEt_2$ or TMSCl were synthetically unsuccessful. However, the use of the cuprate reagent derived from **10** in conjunction with both $BF_3{\cdot}OEt_2$ and PBu_3 was uniquely successful among the reagent combinations explored.

Scheme 2[a]



[a] Reagents: (a) (i) NaH, HMPA−THF, CH_3I (95%). (ii) NaOEt, EtOH. (iii) LAH, Et_2O (90% two steps). (iv) TMSCl, imidazole, CH_2Cl_2 (93%). (b) (i) **7**, *t*-BuLi, CuCN, Et_20 (82%). (ii) TsOH (cat), MeOH−CH_2Cl_2 (94%). (c) (i) CrO_3, H_2SO_4, H_2O, acetone. (ii) K_2CO_3, EtI, acetone (81% two steps). (d) *t*-BuOK, EtOH, (72%). (e) (i) **10**, *t*-BuLi, CuI (0.5 equiv), PBu_3, BF_3·OEt_2, Et_2O-THF (86%). (ii) LAH, Et_2O (91%). (iii) TMSCl, DMAP, Et_3N, CH_2Cl_2 (86%). (iv) $SOCl_2$, py (89%). (f) (i) TBAF, THF (88%). (ii) PCC, silica gel, CH_2Cl_2 (91%). (iii) $(MeO)CH_2PPh_3Cl$, KHMDS, THF (71%). (iv) 1 N HCl, dioxane (91%). (g) 3-lithiofuran, THF (82%). (h) O_2, Rose bengal, *i*-Pr_2NEt, 28 W fluorescent lamp, CH_2Cl_2 (78%).

ether with acid revealed aldehyde **6**. Thereafter, the total synthesis of dysidiolide was realized as previously described.[4,5,7,8] This involved treatment of the aldehyde **6** with 3-lithiofuran to provide the epimeric alcohols **12** and *epi*-**12**, followed by photooxidation[15] of the furan ring of **12** with singlet oxygen to provide (±)-dysidiolide, which gave characterization data that matched those reported for the natural product.

In conclusion, we have demonstrated a novel and concise total synthesis of dysidiolide that is characterized by a high level of intramolecular stereoinduction. Furthermore, the synthetic potential of enone **3** for the synthesis of the iridals[16] and that of enone **5** for the synthesis of the cacospongionolides[17] is apparent.

Acknowledgment. We gratefully acknowledge AstraZeneca, Bristol-Myers Squibb, and the Parker Hughes Institute for their generous unrestricted financial research support. We thank Dr. Gunaskera for kindly providing a comparison sample of naturally occurring **1**.

Supporting Information Available: Experimental procedures and characterization data for all compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006376Z

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