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Stereoselective Synthesis of the Core Structure of the Protein Phosphatase Inhibitor Dysidiolide

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Abstract: The core structure of the protein phosphatase inhibitor dysidiolide and analogs thereof were built up in high yields and with high diastereomer ratios by Diels-Alder reaction between an appropriate diene and an α,β-unsaturated aldehyde.

The progression of cells through the cell cycle is controlled at individual checkpoints. In particular, the transition of cells between the different stages of the cell cycle is mediated by a well balanced interplay between protein kinases and protein phosphatases.[1] For the study of the cell cycle and its regulation at the molecular level highly selective inhibitors of individual protein kinases and protein phosphatases may be efficient reagents.[2] In the course of a program directed at the synthesis and use of natural products and analogs thereof that mediate intracellular signalling events,[3-6] we embarked on a total synthesis of dysidiolide **1**.[7] This sesterterpene from the marine sponge *Dysidea etheria* de Laubenfels[8] inhibits the protein phosphatase Cdc25A (IC_{50} = 9.4 μm) that plays a crucial role in the regulation of the cell cycle at the G_1/S transition.[9] It is cytotoxic to human lung carcinoma cells and murine leukemia cells, probably due to inhibition of Cdc25A.[8] Therefore dysidiolide and analogs thereof are considered interesting, new reagents for the study of cell cycle regulation and as possible agents for the treatment of proliferative diseases like cancer, leukemia and psoriasis.

In a retrosynthetic sense we reasoned that the highly functionalized γ-hydroxybutenolide side chain of dysidiolide might be build up by oxidative elaboration of a furan ring[10] (Scheme 1). As key step for the construction of the bicyclic core structure of the natural product we intended to use a Diels-Alder reaction. By analogy to earlier investigations of related systems[11] triene **4** and aldehyde **5** should undergo an *endo*-selective cycloaddition establishing three of the five required stereocenters in one step (Scheme 1). Subsequently, deoxygenation of the aldehyde and elaboration of the alcohol side chain would permit completion of the synthesis. Given the usually pronounced efficiency of the Diels-Alder reaction and the ready accessibility of appropriate dienes and dienophiles, if successful this strategy should give efficent access to the natural product and various analogs with modified biological properties.

Very recently two total syntheses[12,13] of dysidiolide were reported. One of them independently employed a Diels-Alder strategy very similar to our plan delineated in Scheme 1 as the key step.[13] This coincidence prompts us to disclose in this communication our results on stereoselective Diels-Alder reactions giving rise to the core structure of dysidiolide and analogs thereof.

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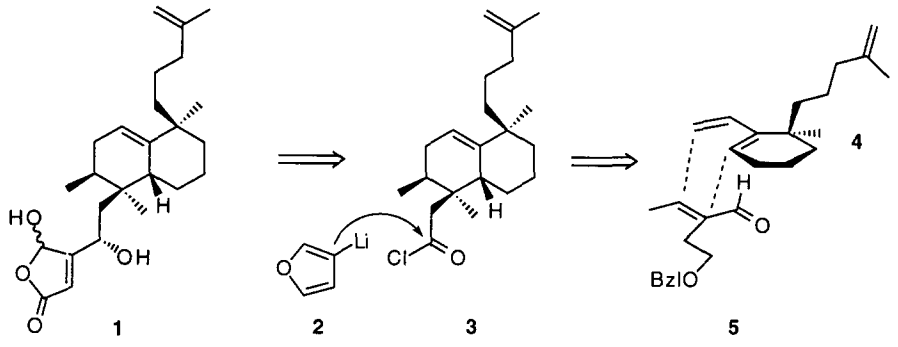
Scheme 1



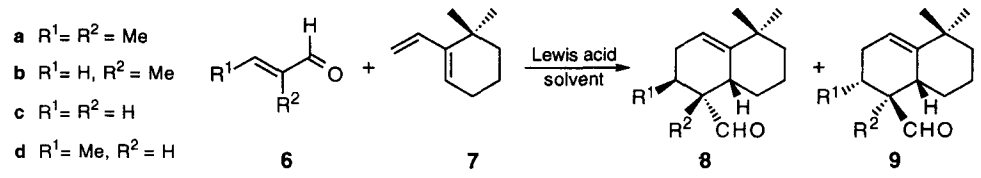
In order to determine the regio- and stereoselectivity of the cycloaddition the Diels-Alder reactions between model diene **7** and the α,β-unsaturated aldehydes **6a** - **6d** were investigated (Scheme 2). If the dienophile **6a** was treated with the diene **7** in the presence of a Lewis acid the cycloadducts **8** and **9** were formed. Depending on the Lewis acid and the solvent used yield and diastereomer ratio varied considerably (Table 1). Whereas $SnCl_4$ in CH_2Cl_2 gave only a very unsatisfying result, both yield and isomer ratio were significantly improved if $ZnCl_2$ in ether or Et_2AlCl in toluene were employed (Table 1, entries 1-3). The best result was observed if a catalyst formed of $EtAlCl_2$ and one equivalent of THF was used at -20 to 0 °C in CH_2Cl_2 as solvent (Table 1, entry 4). This catalyst had already proven fruitful in a synthesis of mamanuthaquinone employing the diene **7** and an α,β-unsaturated ketone.[14] Under these conditions the cycloadducts **8** and **9** were obtained in 85% yield and with a diastereomer ratio of 91:9.[15]

In order to determine how the substitution pattern of the aldehyde influences the outcome of the cycloaddition, aldehydes **6b** - **6d** were subjected to the Diels-Alder reaction with the diene **7** in the presence of $EtAlCl_2$ • THF (Scheme 2, Table 1). Methacrolein **6b** displayed the highest selectivity and gave cycloadduct **8b** with nearly complete stereoselectivity. For acrolein **6c** a lower diastereomer ratio was recorded and crotonic aldehyde **6d** yielded the stereoisomeric products as a 70 : 30 isomer mixture (Table 1, entries 5 - 7). Methacrolein **6b** and acrolein **6c** showed the highest reactivity. In these cases the reactions were complete even at -78 °C in 30 min. Tiglic aldehyde **6a** reacted slower and crotonic aldehyde was slowest. Obviously, introduction of an alkyl group at C-2 of the dienophile leads to a faster reaction and higher selectivity, whereas an alkyl group at C-3 has a rate- and selectivity-decreasing effect.

Table 1: Results of the Lewis acid mediated Diels-Alder reactions employing the model diene **7** and the α,β-unsaturated aldehydes **6**.

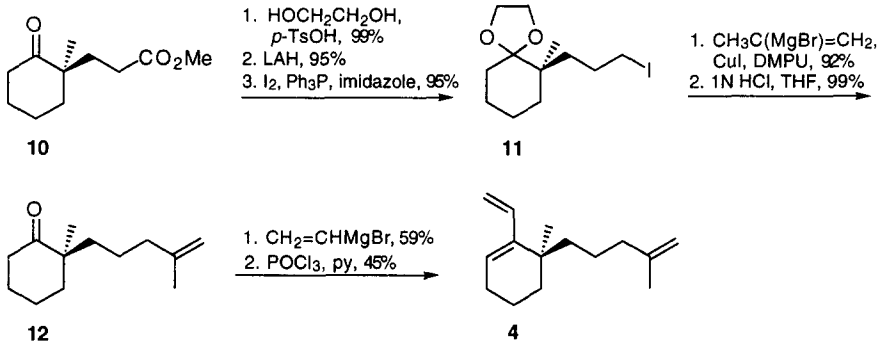
entry No.	dienophile	Lewis acid	solvent	temp. [°C]	reaction time [h]	yield [%]	diastereomer ratio **8 : 9**
1	**6a**	$SnCl_4$	CH_2Cl_2	-20 → 0	3	19	69 : 31
2	**6a**	$ZnCl_2$	Et_2O	25	96	68	74 : 26
3	**6a**	Et_2AlCl	toluene	- 20 → 5	5	68	84 : 16
4	**6a**	$EtAlCl_2$•THF	CH_2Cl_2	-20 → 0	2	85	91 : 9
5	**6b**	„	„	-78	0.5	81	99 : 1
6	**6c**	„	„	-78	0.5	82	94 : 6
7	**6d**	„	„	-30 → 0	3	84	70 : 30

Scheme 2



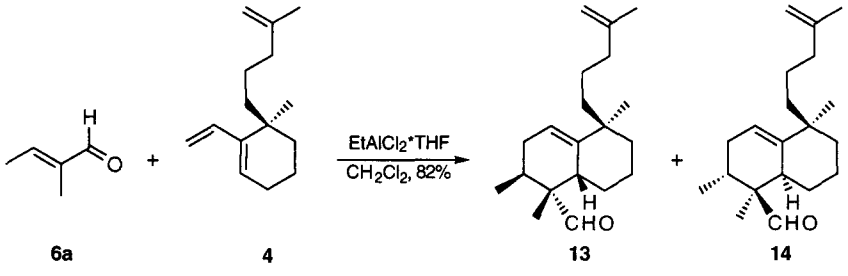
These encouraging results clearly indicated that the core structure of dysidiolide should be accessible via Lewis acid mediated Diels-Alder reaction with a correctly substituted diene in an efficient manner. Therefore the required triene **4** was built up as shown in Scheme 3. To synthesize triene **4**, ketone **10** (90 % ee)[16] was protected as ethylene acetal and then the ester was reduced to the corresponding alcohol which could be converted into the iodide **11** in high yield (Scheme 3). Displacement of the iodide with 2-propenylmagnesium bromide in the presence of catalytic amounts of CuI and subsequent removal of the acetal protecting group yielded ketone **12** efficently. The desired triene finally was constructed by addition of vinylmagnesium bromide to the carbonyl group of **12** and subsequent dehydration by treatment with $POCl_3$ in pyridine.

Scheme 3



Triene **4** and tiglic aldehyde **6a** reacted smoothly at -30 to 0 °C in the presence of $EtAlCl_2$•THF to give the desired cycloadducts in 82 % combined yield (Scheme 4).[17] Similar to the result recorded for diene **7** the *endo:exo* ratio was 93 : 7.[15] The stereodirecting influence of the stereocenter in **4** was, however, only relatively weak. Thus the two *endo*-isomers **13** and **14** (Scheme 4), which result from attack of the dienophile from the face of the diene opposite to the alkenyl side chain, and the corresponding stereoisomer which results from attack opposite to the methyl group were formed in a ratio of 2:1. Boukouvalas *et al.*[13] recorded a very similar diastereomer ratio for the Diels-Alder reaction between a closely related diene and dienophile.

Scheme 4



The cycloadduct **13** embodies four of the five stereocenters found in dysidiolide. Tiglic aldehyde **6a** is very similar to aldehyde **5** required for the synthesis of the natural product delineated in Scheme 1, and aldehydes with similar structures (e.g. **6b** - **6d**) react readily with dienes like **4** and **7**. These findings suggest that numerous analogs of the natural product which may display very interesting and useful biological proporties should be efficiently accessible by employing the Diels-Alder strategy described in this paper as the key transformation.

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15. The diastereomeric ratio was determined by integration of the signals recorded for the vinylic protons in the ^{1}H NMR spectra. The *endo*-configurations of the major isomers were established by NOESY experiments (500 MHz, $CDCl_3$).
16. Ketone **10** and its enantiomer are commercially available (ee 99%) or easily prepared from racemic 2-methylcyclohexanone and (S)-(-)- or (R)-(+)-1-phenylethylamine in a two-step procedure: M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *Tetrahedron Asymm.* **1992**, *3*, 459.
17. Procedure for the Diels-Alder reaction between triene **4** and tiglic aldehyde **6a**: To a solution of tiglic aldehyde **6a** (125 mg, 1.48 mmol) and THF (125 µl, 1.48 mmol) in 5 ml of CH_2Cl_2 was added under argon at -30°C a 1M solution of $EtAlCl_2$ in hexane (1.48 ml, 1.48 mmol). After 5 min a solution of triene **4** (151 mg, 0.76 mmol) in 2 ml of $CH_2Cl_2$was added and the mixture was allowed to warm up to 0°C during 3 h, (the progress of the reaction was monitored by GCMS). After addition of sat. NH_4Cl (5ml) the organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2 (10 ml). The combined organic layers were washed with 1N HCl, sat. $NaHCO_3$ and dried with $MgSO_4$. After filtration and evaporation of the solvent the residue was purified by column chromatography (silica gel, pentane/ether = 20/1) to give a mixture of **13** and **14** (175 mg, 82%).[15]
13: colorless oil, R_f = 0.35 (pentane/ether = 20/1). ^{1}H NMR (500 MHz,$CDCl_3$) δ (ppm): 0.85 (d, J = 6.5 Hz, 3H, 2-CH_3), 0.95 (s, 3H, 1-CH_3), 1.00 (s, 3H, 5-CH_3),1.02-1.06 (m, 1H, 1'-H_a), 1.07-1.16 (m, 1H, 2'-H_a), 1.21 (dt, J = 13 Hz, J = 4.5 Hz, 1H, 6-H_a), 1.24-1.33 (m, 1H, 2'-H_b), 1.37 (dt, J = 12 Hz, J = 4.5 Hz, 1H, 8-H_a), 1.49-1.54 (m, 1H, 6-H_b), 1.54-1.67 (m, 2H, 7-H), 1.68-1.79 (m, 3H, 3-H_a, 8-H_b, 1'-H_b), 1.69 (s, 3H, 4'-CH_3), 1.96 (q, J = 7 Hz, 2H, 3'-H), 2.01-2.05 (m, 1H, 8a-H), 2.12-2.21 (m, 2H, 3-H_b, 2-H), 4.64 (s, 1H, 5'-H_a), 4.68 (s, 1H, 5'-H_b), 5.36 (s, 1H, 4-H), 9.67 (s, 1H, CHO).^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 14.0 (1-CH_3), 16.1 (2-CH_3), 22.0 (C-7), 22.2 (C-2'), 22.3 (4'-CH_3), 26.2 (5-CH_3), 28.1 (C-2), 30.5 (C-8), 31.1 (C-3), 36.6 (C-1'), 38.6 (C-3'), 39.8 (C-1), 41.8 (C-6), 43.0 (C-8a), 50.2 (C-5), 109.8 (C-5'), 117.2 (C-4), 143.6 (C-4a), 146.1 (C-4'), 209.8 (CHO). FTIR (KBr) $\tilde{\nu}$ (cm^{-1}): 3073, 3052, 1726, 1649. EIMS (70 eV) m/z (%): 288 (11) [M^+], 259 (93), 206 (44), 177 (100), 161 (19), 147 (17), 121 (32). HRMS Calc. 288.2453, Found. 288.2466.