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Design, synthesis and cytotoxicity of 7-deoxy aryl discodermolide analogues

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Abstract—A series of 7-deoxy discodermolide analogues in which the lactone fragment '**C**' was replaced by aryl substituents were designed, synthesized, and evaluated for cytotoxicity.

Discodermolide (+)-**1** (Fig. 1), a polyketide natural product isolated from the marine sponge *Discodermia dissoluta*,[1] has potent growth inhibitory activity against human tumor cell lines.[2,3] The mode of action, similar to that of paclitaxel, involves the assembly and stabilization of microtubules, leading to mitotic arrest and, ultimately, to cell death.[2,3] Attempts to acquire practically useful quantities of (+)-discodermolide, either by cultivation of the producing sponge, or via harvesting of the organism in the wild have thus far failed; therefore totally synthetic (+)-**1** was necessary to permit human clinical trials.[4,5]

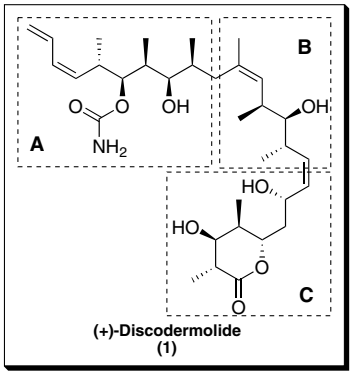

Figure 1.

A number of groups have reported total syntheses of (+)-discodermolide (**1**).[6] In addition, a large number of analogues have also been disclosed,[6c,g,7] some of which are significantly truncated yet retain considerable cytotoxic activity. Although the majority of these compounds do not show the level of cell growth inhibitory potency required to support further preclinical investigation, the potential benefits of more synthetically accessible compounds continues to fuel significant research efforts.

The previously reported (+)-2,3-dehydrodiscodermolide analogue **2**[7a] (Fig. 2) displays in vitro cytotoxicity

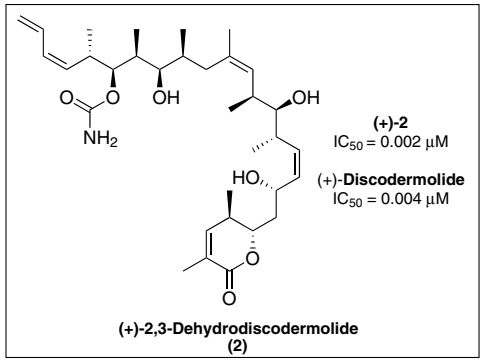

Figure 2.

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activity superior to that of the parent discodermolide when evaluated against the A549 human lung carcinoma cell line. Based on this data we reasoned that the '**C**' region of (+)-discodermolide (Fig. 1) could be further simplified while preserving significant cell growth inhibitory activity. Our investigation began with the Wittig union of the previously reported salt (+)-**3**[6f] and hydrocinnamaldehyde (**4a**), followed by oxidative removal of the PMB ether, carbamate installation, and global deprotection, yielding the considerably simplified derivative (+)-**6a** (Scheme 1, $R_1{=}R_2 = H$) in which the entire **C**-region has been replaced with a phenylethylene substituent. Pleasingly, this analogue retained considerable cytotoxic potency in four human tumor cell lines (Table 1), despite the removal of *five* stereogenic centers.

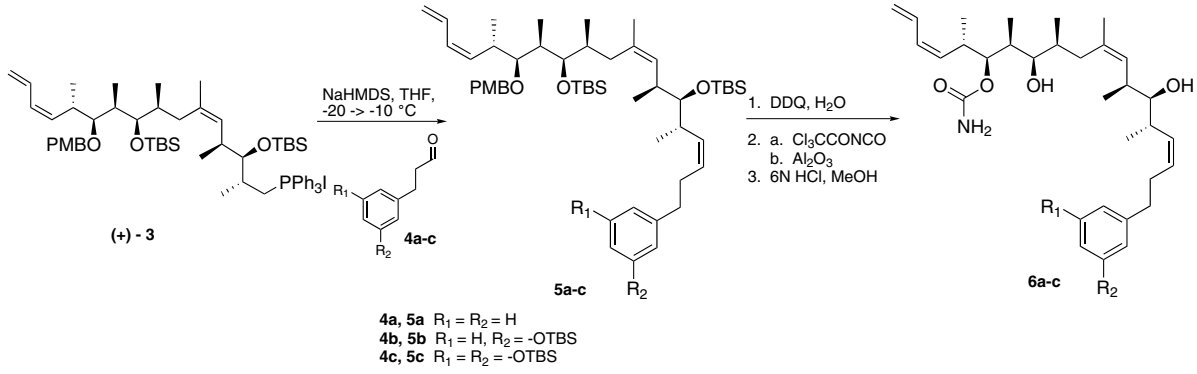
Reincorporation of oxygenation as in **6b** proved to augment activity relative to the unsubstituted case. Comparison of **6b** to the parent (+)-discodermolide suggests that the phenol hydroxyl could mimic either the endocyclic oxygen or the C(3) hydroxyl group, both of which have been implicated in intramolecular hydrogen bonding interactions in the natural product.[8] Further oxygenation as in **6c** provided no additional increase in cytotoxicity.

Seeking to explore further the effect of derivatization of the aromatic substituent, we designed a small library of congeners incorporating a range of functionalized phenyl rings as well as two isosteric thiophenes. Here we surmised that a reversal of the Wittig coupling partners would obviate the necessity for ultrahigh pressure in the formation of the salt (+)-**3**,[6f] providing a more efficient manifold for the production of analogues.

Hence, beginning with the known intermediate (+)-**7**[6f] (Scheme 2), regioselective reduction of the PMP acetal, followed by oxidation of the primary alcohol with the Dess–Martin periodinane[9] provided the aldehyde **8**. Installation of the diene, according to the procedure of Yamamoto and co-workers[10] gave the triene **9**. Oxidative removal of the PMB protecting groups, followed by selective oxidation of the primary alcohol using TEMPO with iodobenzene diacetate as the co-oxidant furnished our desired aldehyde **10**. Wittig coupling of the phosphonium salts **17a–j** (3–5 equiv) gave the aryl alcohols **11a–j** in excellent yields. Treatment of the latter, in turn, with trichloroacetylisocyanate[11] and methanolic potassium carbonate provided the corresponding carbamates. Removal of the *tert*-butyldimethylsilyl protecting groups (TBS) with methanolic HCl gave the final aryl discodermolide analogues **12a–j**.

The requisite phosphonium salts **17a–h** (Scheme 3) were prepared starting from the commercially available (Aldrich) Grignard reagent solutions in THF or ether (**13a–h**). Treatment of the solutions directly with allylbromide led to the allyl adducts **14a–h**. Hydroboration of the olefin followed by a peroxide work-up then gave the aryl propanols **15a–h**. Iodination of the propanols was accomplished using iodine, triphenylphosphine, and imidazole. Subsequent displacement of the primary iodides **16a–j** with triphenylphosphine in toluene at 100 °C completed the construction of the phosphonium salts **17a–j**.

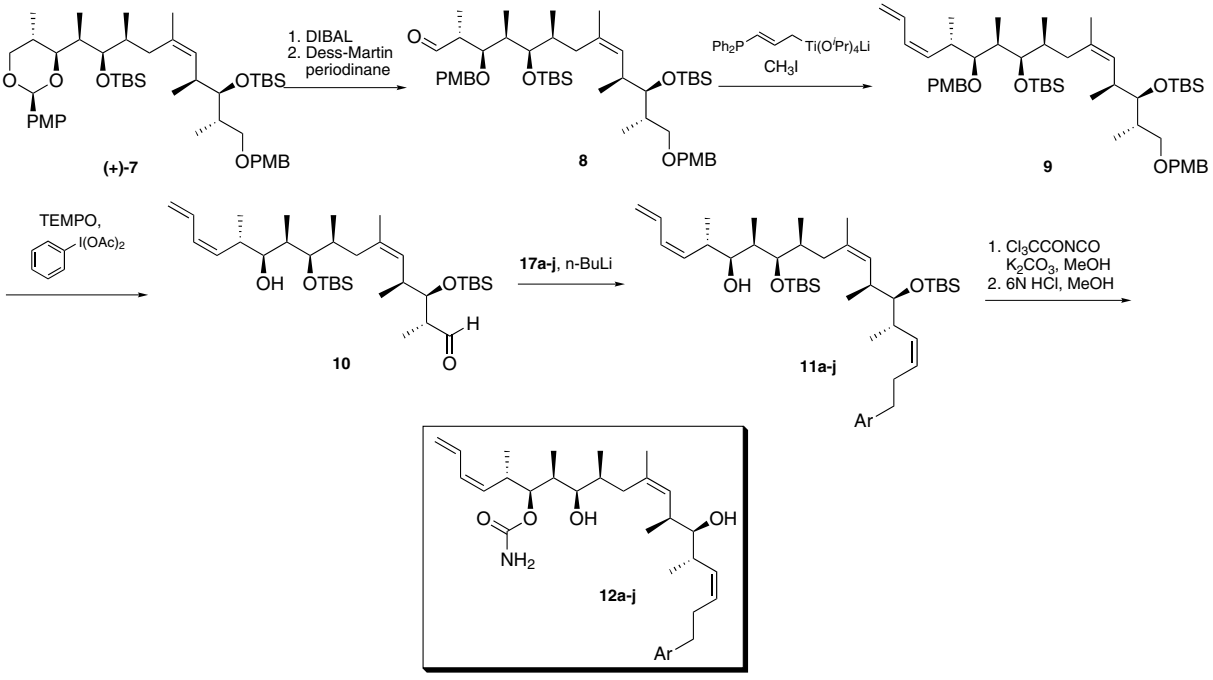
Aryl propanols **15i** and **15j** were synthesized as is shown in Scheme 4. The hydroxyl group of 3-hydroxy-2-methylbenzoic acid **18** was protected as the TBS ether employing the corresponding silyl triflate and triethylamine. The free acid was then treated with trimethylsilyldiazomethane to provide the methyl ester, which was reduced to the corresponding benzylic alcohol using diisobutylaluminum hydride. Catalytic oxidation of the



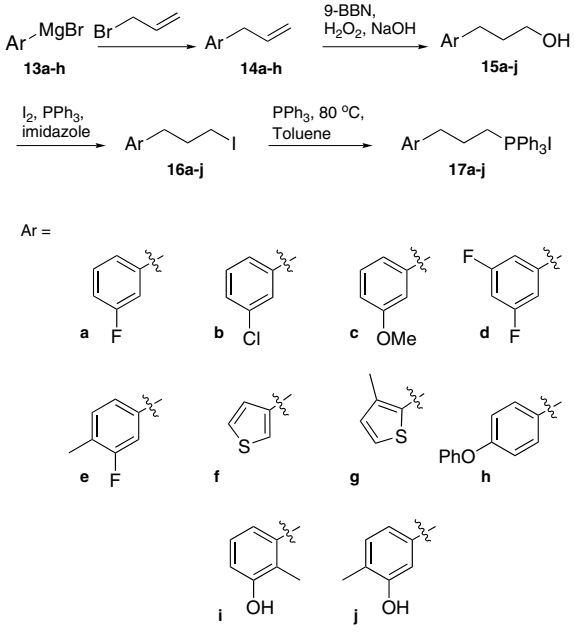
Scheme 1.

Table 1. Cytotoxicity observed for analogues **6a–c**

			Cytotoxicity IC_{50} (μM)			
	R_1	R_2	MCF-7	MCF-7/ADR	A549	SKOV-3
6a	H	H	0.48	0.56	0.51	0.35
6b	H	OH	0.13	0.39	0.19	0.04
6c	OH	OH	0.16	>1.0	0.31	0.04

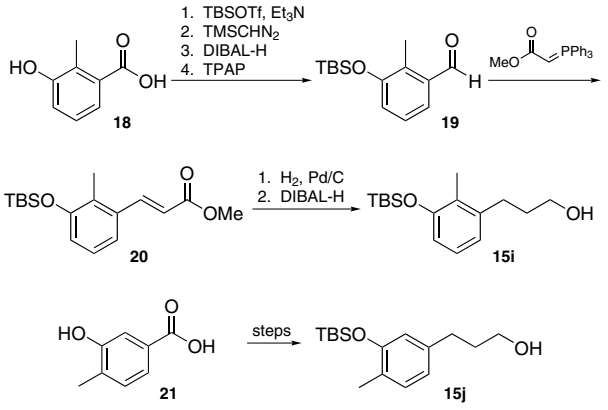


Scheme 2.



Scheme 3.

alcohol using TPAP[12] and *N*-methylmorpholine oxide gave benzaldehyde **19**. Exposure of the aldehyde to (carbomethoxymethylene)triphenylphosphorane led to unsaturated methyl ester **20**, which was reduced in two steps to give the desired aryl propanol **15i**. The related alcohol **15j** was synthesized in an analogous fashion from 3-hydroxy-4-methylbenzoic acid **21**.



Scheme 4.

Table 2. Cytotoxicity observed for analogues **12a**–**j**

	Cytotoxicity IC_{50} (μM)			
Ar	MCF-7	MCF-7/ADR	A549	SKOV-3
12a	0.37	0.50	0.65	0.40
12b	0.40	0.65	0.58	0.38
12c	0.33	0.50	0.60	0.37
12d	0.60	2.0	1.0	0.36
12e	1.0	4.0	4.0	1.0
12f	0.85	4.0	4.0	0.44
12g	0.37	0.62	0.79	0.37
12h	4.0	10.0	10.0	10.0
12i	0.49	1.0	0.91	0.27
12j	0.77	4.0	4.0	0.41

The analogues **12a**–**j** were assayed against four human tumor cell lines (Table 2), including MCF-7/ADR, an adriamycin and paclitaxel resistant cell line, which over expresses the MDR P-glycoprotein. The majority of the analogues display sub-micromolar activity against the

nonresistant cell lines and several retain activity in the resistant line (**6a**,**b**, **12a**–**c**,**g**). The most potent compounds display a range of *meta* substituents (OH, F, Cl, OMe) while maintaining similar activities. The methyl substituted thiophene **12g** also displayed very good activity across the entire panel. However, modest variation of the ring can lead to significant losses in activity as demonstrated by the difluoro analogue **12d**, and the unsubstituted thiophene **12f**. Substitution at the *para* position also appears to be quite sensitive (cf. **12a** vs **12e**, and **12i** vs **12j**). Clearly, opportunities exist in further exploration of the *meta* position; other heterocycles may also permit further enhancements of cytotoxic activity.

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