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Synthesis and biological activity of desmethoxy analogues of coruscanone A

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ABSTRACT

A series of simple desmethoxy analogues of coruscanone A was prepared via a novel version of Ti(*i*PrO)$_4$-mediated Knoevenagel condensation of cyclopentenedione with substituted benzaldehydes and cinnamic aldehydes, and the compounds were evaluated for antifungal activity and cytotoxicity. The most potent 2-benzylidenecyclopent-4-ene-1,3-dione possessed antifungal effect comparable to coruscanone A and a somewhat broader spectrum of activity against *Candida* species. The compound was also superior to fluconazole against several non-albicans *Candida* sp. Evaluation of the ability of the compound to influence cell proliferation using two different assays showed that 2-benzylidenecyclopent-4-ene-1,3-dione has lower cytotoxicity compared to the natural product.

The development of novel antifungal agents is of undisputable importance in view of a significant increase of incidence of invasive fungal infections, especially among hospitalized patients.[1] While the structures of existing drugs, especially those of the azole series[2] are continuously being modified, the realm of natural products has been a permanent source of novel active structures.[3] Undoubtedly, the production and screening of small, natural product-based libraries continues to be an important tool in the identification of new lead structures.[4]

Having described the activity of α-haloaryl γ-alkylidene butenolides,[5] our attention was captured by the report by Clark et al.[6] on the isolation, synthesis and antifungal activity evaluation of a structurally similar natural cyclopentenedione, coruscanone A and several of its derivatives (Fig. 1). The natural product was found to possess in vitro antifungal activity comparable to amphotericin B, albeit in terms of μg/mL, and acceptable toxicity against Vero and LLC-PK1 cells (4.9 and 3.4 μg/mL, respectively).

The relationship between γ-alkylidene butenolides and coruscanone A is shown in Scheme 1, arising from a base-catalyzed rearrangement of the former into the latter. Hence, the possibility of the same or related mechanism of action was envisioned.

Clark et al. have also investigated[7] the importance of several substructural fragments for antifungal activity, namely the cyclopentenedione ring, enolic methoxy group and styryl moiety (Fig. 1). Based on the exploration of structure-antifungal activity relationships of a number of synthetic analogues, they concluded that (1) alterations of the methyl groups (both that on the cyclopentenedione ring and the enolic methoxy group) reduce in vitro antifungal activity, (2) replacement of the styryl moiety by a phenyl or methyl group also leads to a dramatic drop in the activity, and (3) *p*-substitution of the benzene ring or its replacement with five-membered heterocycles maintains the activity of the com-

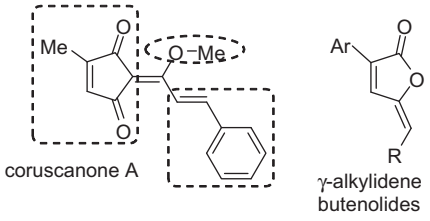
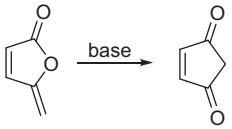


Figure 1. Structures of coruscanone A and γ-alkylidene butenolides.



Scheme 1. Rearrangement of γ-alkylidene butenolide into cyclopentenedione.

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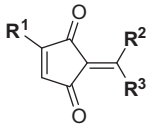


R1 = Me, **R2** = OH, OMe (ref. 7)
R1, R2 = H (this work)

Figure 2. General structure of the compounds studied.

pounds at a level similar to the parent coruscanone A. However, even though a number of analogues were prepared, the activities of the most promising ones were only comparable to coruscanone A, and antifungal activity was always accompanied by various degrees of cytotoxicity against the above-mentioned cell lines.

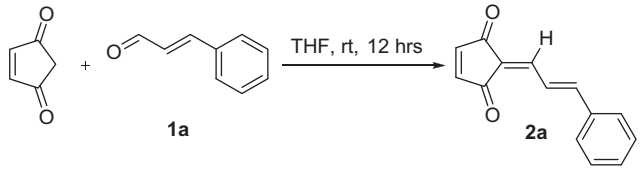
Interestingly, even though Clark and co-workers concluded[7] that the cyclopentenedione moiety acts through its Michael accepting ability, no attempt to prepare analogues with an unsubstituted cyclopentene double bond that would be even more easily accessible by nucleophiles has been reported. Similarly, the SARs clearly showed the importance of the methoxy group (as compared to a free hydroxyl) for antifungal activity, but no deoxy derivatives have been prepared.[8] Since such compounds would be easy to make via simple Knoevenagel condensations of cyclopent-4-ene-1,3-dione with aldehydes, we set out to prepare a series of simple Knoevenagel adducts with a variety of substituted cinnamaldehydes and benzaldehydes, and to evaluate the antifungal effect of the derivatives (Fig. 2).

Knoevenagel condensation is a classical transformation that is commonly carried out in basic media. However, basic conditions are incompatible with the conjugated enone nature of the substrate, which undergoes fast polymerization[9] upon treatment with a base. Prior to this work, only two papers describing a successful Knoevenagel condensation of cyclopent-4-ene-1,3-dione with benzaldehyde[9] and cinnamaldehyde[10] had been published, both using a large excess (20 equiv) of $BF_3{\cdot}OEt_2$. Even though the yields reported were as high as 50%, in our hands the reaction repeatedly afforded isolated yields $\leqslant$10%. In addition, the large excess of the Lewis acid made the workup somewhat tedious. Since we intended to prepare adducts with a number of aldehydes, we sought a more user-friendly reagent that would deliver the Knoevenagel adduct in a catalytic fashion in more acceptable yields.

A number of acids have been described as Knoevenagel reaction promoters, including classical acidic reagents such as $CeCl_3{\cdot}7\ H_2O$/NaI,[11] $HClO_4$–SiO_2,[12] $TiCl_4$,[13] $ZnCl_2$,[14] $NbCl_5$[15] as well as rare earth metal salts such as $Yb(OTf)_3$.[16] Some of the reagents were apparently too harsh for sensitive compounds ($TiCl_4$), while others ($NbCl_5$, $Yb(OTf)_3$) seemed too costly given the simple nature of the transformation. Even though some of the above reagents were included in the screening for a suitable Lewis acid catalyst, our aim was to identify an easily accessible, low cost reagent. As shown in Table 1, 0.3 molar equivalents of Ti(*i*PrO)$_4$ together with an excess of the aldehyde enabled us to prepare compound **2a** in an acceptable, 64% isolated yield. Increasing the amount of the Lewis acid had no appreciable effect, while decreasing led to a somewhat lower yield. Similar results were obtained using $Cu(OTf)_2$. The use of more expensive $Yb(OTf)_3$ or $AuCl_3$ in lower loadings (0.1) did not lead to satisfactory yields. Solvent screening revealed that THF provided the best medium for the transformation.

As regards the mechanism of the reaction, it is interesting to note that no changes in chemical shifts were observed upon monitoring an equimolar mixture of cyclopent-4-ene-1,3-dione with Ti(*i*PrO)$_4$ in THF-d_8 by NMR. It would therefore seem that the Lewis acid activates the aldehyde component and coordinates both partners together. A tentative transition state derived from these consider-

Table 1
Lewis acid screening



Entry	LA	Amount of LA	Isolated yield[a] (%)
1	$BF_3{\cdot}OEt_2$	20.0	$\leqslant$10
2	$Cu(OTf)_2$	0.3	56
3	Ti(O*i*Pr)$_4$	0.2	57
4	**Ti(O*i*Pr)$_4$**	**0.3**	**64**
5	Ti(O*i*Pr)$_4$	0.5	64
6	$AuCl_3$	0.1	5
7	$Yb(OTf)_3$	0.1	30
8	Et_2AlCl	0.3	0

[a] 3.0 equiv of cinnamaldehyde were used.

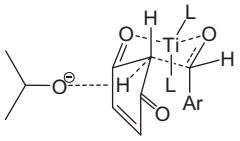
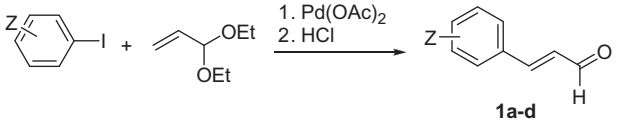


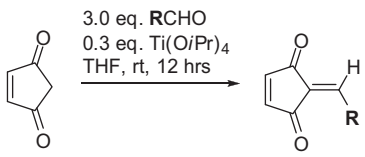
Figure 3. Tentative transition state for the condensation.



Product:	**Z**:	Isolated yield (%)
1a	4-OCH_3	70
1b	4-CH_3	58
1c	4-Cl	61
1d	4-NO_2	47

Scheme 2. Preparation of substituted cinnamic aldehydes.

Table 2
Overview of the prepared compounds



Entry	R	Product	Isolated yield (%)
1	Ph-CH=CH–	**2a**	64
2	4-MeOPh-CH=CH–	**2b**	21
3	4-MePh-CH=CH–	**2c**	36
4	4-ClPh-CH=CH–	**2d**	30
5	4-NO_2Ph-CH=CH–	**2e**	0
6	Ph	**2f**	43
7	4-MeOPh	**2g**	31
8	4-MePh	**2h**	49
9	4-ClPh	**2i**	49
10	4-FPh	**2j**	25
11	4-BrPh	**2k**	57
12	3-BrPh	**2l**	31
13	4-$(Me)_2$NPh	**2m**	10
14	4-NO_2Ph	**2n**	0
15	2-Furyl	**2o**	70
16	3-Furyl	**2p**	0
17	2-Thienyl	**2q**	45
18	2-Naphthyl	**2r**	22

ations is shown in Figure 3. The cyclopentenone double bond as well as the aldehyde aryl moiety must also play important roles, since cyclopentane-1,3-dione did not react with benzaldehyde and cyclopent-4-ene-1,3-dione did not afford any addition products with aliphatic aldehydes under the conditions described in Table 1, entry 4.

Having developed a suitable protocol, a number of 2-alkylidenecyclopent-4-ene-1,3-diones with substituted phenyl, substituted styryl and heteroaryl moieties were prepared under the same conditions. Substituted cinnamic aldehydes **1a**–**d**, which were not commercially available, were prepared[17] via the Heck reaction of substituted phenyl iodides with 3,3-diethoxypropene (Scheme 2).

The results summarized in Table 2 show that a substitution of the phenyl ring generally decreases yields. This trend is more pronounced for strong electron donors, even though the presence of the strongly electron withdrawing NO_2 group inhibited the reaction completely. The yields of heteroaryl derivatives depend on the nature of the heterocycles and position of the carbaldehyde group. While furan-2-carbaldehyde furnished the highest yield of alkylidene product **2o**, its 3-isomer (**2p**) did not react at all.

Since the compounds were prepared for screening purposes, no further optimization was attempted.

All compounds were subjected to screening for antifungal activity[18] on a panel of both yeasts and filamentous fungi (Table 3). For the purpose of a brief SAR evaluation, the antifungal activities expressed as IC_{80} were compared to coruscanone A as the parent structure, and also to fluconazole as a drug standard. Surprisingly, unsubstituted compound **2a** with styryl side chain possessed significant activity against *Candida albicans* ATCC44859 strain, comparable to coruscanone A, and was superior to the natural product against *Candida krusei* and *Candida glabrata*. Thus, complete removal of the methoxy group had very little effect on in vitro antifungal activity, even though further substitution of the phenyl ring meant a significant drop of biological effect. Appreciable activity was detected only for the 4-methylstyryl derivative **2c**, while the 4-OMe and 4-Cl styryl derivatives **2b** and **2d** were practically inactive ($IC_{50} \geqslant 62.5$).

Also surprisingly, when the styryl double bond was removed, the compounds retained antifungal effect, and the activities of the unsubstituted phenyl derivative **2f** were slightly higher than those of its styryl counterpart **2a**, especially against *Candida tropicalis*, *C. glabrata* and *Trichosporon asahii*. Similar to the styryl analogues, substitution of the aryl ring also had a negative effect on

Table 3
Antifungal activities of **2a**–**r**, coruscanone A and fluconazole

Compound	Time (h)	CA1[a]	CA2[b]	CP[c]	CK1[d]	CK2[e]	CT[f]	CG[g]	CL[h]	TA[i]	AF[j]	AC[k]	TM[l]
2a	24	1.95	15.62	3.9	3.9	15.62	7.81	15.62	7.81	7.81	31.25	>125	7.81
	48	1.95	15.62	7.81	7.81	15.62	15.62	31.25	15.62	15.62	31.25	>125	62.5
2b	24	125	250	250	250	250	250	250	250	250	250	>500	250
	48	250	250	250	250	250	250	250	250	500	250	>500	500
2c	24	3.9	7.81	7.81	7.81	7.81	7.81	31.25	7.81	31.25	62.5	>125	125
	48	7.81	7.81	31.25	15.62	15.62	7.81	31.25	15.62	>125	>125	>125	>125
2d	24	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	>250	62.5
	48	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	125	125	>250	250
2f	24	1.95	3.9	3.9	3.9	3.9	3.9	7.81	7.81	1.95	15.62	250	1.95
	48	1.95	7.81	3.9	3.9	7.81	3.9	7.81	15.62	3.9	31.25	250	3.9
2g	24	3.9	7.81	7.81	3.9	3.9	7.81	7.81	7.81	7.81	15.62	>250	3.9
	48	7.81	7.81	15.62	3.9	7.81	7.81	7.81	31.25	31.25	31.25	>250	7.81
2h	24	3.9	3.9	15.62	7.81	15.62	7.81	15.62	15.62	15.62	31.25	>250	125
	48	7.81	15.62	15.62	15.62	15.62	15.62	15.62	15.62	62.5	125	>250	>250
2i	24	7.81	31.25	31.25	31.25	31.25	31.25	62.5	31.25	31.25	62.5	>125	125
	48	31.25	31.25	31.25	31.25	62.5	31.25	62.5	31.25	62.5	62.5	>125	>125
2j	24	7.81	15.62	15.62	15.62	15.62	15.62	31.25	15.62	31.25	31.25	>125	15.62
	48	15.62	31.25	31.25	31.25	31.25	31.25	31.25	31.25	62.5	62.5	>125	15.62
2k	24	7.81	15.62	15.62	15.62	15.62	15.62	15.62	15.62	15.62	31.25	>125	15.62
	48	15.62	15.62	15.62	15.62	15.62	15.62	15.62	15.62	15.62	31.25	>125	15.62
2l	24	15.62	15.62	31.25	15.62	31.25	31.25	31.25	31.25	32.5	125	>125	15.62
	48	31.25	31.2	62.5	31.25	31.25	62.5	62.5	31.25	125	125	>125	15.62
2m	24	31.25	31.25	3.9	7.81	7.81	62.5	62.5	7.81	7.81	15.62	>125	0.98
	48	31.25	62.5	7.81	7.81	7.81	>125	>125	31.25	15.62	31.25	>125	0.98
2o	24	7.81	15.62	15.62	7.81	15.62	15.62	15.62	15.62	15.62	15.62	250	7.81
	48	15.62	15.62	15.62	15.62	15.62	15.62	15.62	15.62	31.25	31.25	>500	7.81
2q	24	7.81	15.62	15.62	7.81	7.81	15.62	7.81	15.62	15.62	15.62	500	15.62
	48	7.81	15.62	15.62	15.62	7.81	15.62	15.62	15.62	31.25	15.62	>500	15.62
2r	24	15.62	15.62	15.62	15.62	31.25	31.25	31.25	15.62	15.62	15.62	125	7.81
	48	15.62	15.62	15.62	31.25	31.25	31.25	31.25	15.62	62.5	31.25	>125	15.62
CorA[m]	24	0.98	NT[n]	NT	NT	125	3.91	125	NT	0.98	31.25	31.25	3.91
	48	3.91	NT	NT	NT	250	7.1	125	NT	7.81	250	250	7.81
FLU[o]	24	1	0.8	6.5	>50	>50	3	22	3.3	4	>50	>50	17
	48	2	3.3	13	>50	>50	5	>50	3.3	9	>50	>50	26

[a] *Candida albicans* ATCC44859.
[b] *C. albicans* ATCC90028.
[c] *C. parapsilosis* ATCC22019.
[d] *C. krusei* ATCC 6258.
[e] *C. krusei* E28.
[f] *C. tropicalis* 156.
[g] *C. glabrata* 20/I.
[h] *C. lusitaniae* 2446/I.
[i] *Trichosporon asahii* 1188.
[j] *Aspergillus fumigatus* 231.
[k] *Absidia corymbifera* 272.
[l] *Trichophyton mentagrophytes* 445 (MIC values were determined after 72 and 120 h).
[m] Coruscanone A.
[n] NT = not tested.
[o] Fluconazole.

antifungal action of the compounds, albeit not so dramatic. Only the 4-methoxyphenyl compound **2g** was comparable to **2f** for most species, with the exception of *C. albicans ATCC44859*, *Candida parapsilosis* and *T. asahii*, for which somewhat higher MICs were recorded. 4-methylphenyl substance **2h** displayed the same inhibitory effect as the 4-methoxyphenyl derivative **2g** against *C. albicans ATCC44859*, and there are no significant differences for most other strains, with the exception of *C. krusei ATCC 6258*, *Aspergillus fumigatus* and *Trichophyton mentagrophytes*. On the whole, however, the profile of activity of **2h** is worse than those of **2f** and **2g**, and the same applies to haloaryl compounds **2i**–**l**, the effects of which are even lower. A partial exception was the 4-dimethylaminophenyl substance **2m** with better MIC values against both *C. krusei* strains, *C. parapsilosis* and *T. mentagrophytes*.

As regards the derivatives with a different aryl than phenyl (**2o**–**r**), their MICs were also higher than those of unsubstituted styryl and phenyl derivatives **2a** and **2f**.

The in vitro activities of the most effective derivative **2f** were comparable to coruscanone A against *C. albicans*, *C. tropicalis* and *T. asahii*, and better than those of the natural product against *C. krusei*, *C. glabrata* and *A. fumigatus*. Hence, the deoxygenation of the methoxy function combined with the removal of the styryl double bond in the natural product has very little influence on the biological activity, and the simple benzylidene analogue has a broader spectrum of activity against *Candida* strains. Compound **2f** (and, in some cases, coruscanone A as well) is in vitro clearly superior to fluconazole against *non-albicans Candida* sp., namely *C. parapsilosis*, *C. krusei*, and *C. glabrata*, and comparable to the drug against *C. albicans*, *C. tropicalis* and *C. lusitaniae*. In line with the conclusions by Clark et al, further substitution of the phenyl ring generally led to a decrease in the activity. However, unlike the previously described[7] methoxy derivatives, the drop in the activity for the substituted styryl analogues described herein was much more pronounced, as demonstrated by the loss of activity of **2b** and **2d**. On the other hand, the activities of the substituted benzylidene derivatives **2g**–**m** were not far from that of unsubstituted **2f**. The high in vitro antifungal effect of **2f** is a possible indication that the compounds of the simple benzylidene series described in this paper may bind in a different way to the target protein, since methoxy compound **3**[7] (Fig. 4) lacking the styryl double bond was inactive. However, Michael addition of a nucleophile also seems to be the major driving force behind the interaction with a cellular target.

All compounds were also subjected to screening on a panel of cancer cell lines, including three types of leukemic cells and three solid tumors[19]; cell viability was quantified using XTT standard spectrophotometric assay[20] (Table 4). A majority of the new compounds possessed moderate IC_{50} values (micromolar range) against the CCRF-CEM line, and four of them also against HeLa cells. The most active derivative **2f** inhibited the growth of just the CCRF-CEM cells, while moderate IC_{50} values against all leukemic lines used in this study were recorded for coruscanone A.

In addition, all compounds were subjected to a preliminary kinetic cell-based morphological screening.[21] In this experiment, impedance readout was used for monitoring the effect of the compounds on the proliferation of HEK293 cells (human embryonal kidney cells). With the exception of coruscanone A and compounds **2a**, **2c** and **2k**, for which a cytostatic-like action was recorded (a mild decrease in proliferation, followed by a slow rise and plateauing), no effect was observed. This, taken together with the results of screening for cytostatic activity shown in Table 4 could be an indication that, compared to the previously prepared derivatives,[7] the cytotoxicity of the desmethoxy compounds described herein may be reduced.

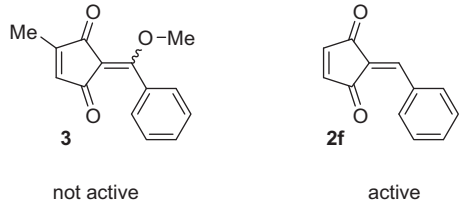


Figure 4. Comparison of **3** and **2f**.

Table 4
Cytostatic activities

Compd	L1210[a]	HL 60[b]	HeLa S3[c]	CCRF-CEM[d]	HT-29[e]	Colo 201[f]
2a	NA[g]	NA	NA	4.4 ± 0.2	NA	NA
2b	NA	NA	NA	NA	NA	NA
2c	NA	NA	7.3 ± 0.2	NA	NA	NA
2d	NA	NA	NA	NA	NA	NA
2f	NA	NA	NA	2.6 ± 0.2	NA	NA
2g	NA	NA	NA	3.8 ± 0.2	NA	NA
2h	NA	NA	NA	2.7 ± 0.2	NA	NA
2i	NA	NA	NA	6.1 ± 0.4	NA	NA
2j	NA	NA	NA	1.6 ± 0.1	NA	NA
2k	NA	NA	4.9 ± 0.8	1.8 ± 0.3	NA	NA
2l	NA	NA	NA	7.5 ± 0.5	NA	NA
2m	NA	NA	NA	4.3 ± 0.1	NA	1.3 ± 0.1
2o	NA[g]	NA	5.4 ± 0.7	2.5 ± 0.3	NA	NA
2q	NA	NA	NA	4.2 ± 0.2	NA	NA
2r	NA	NA	13.5 ± 1.1	3.7 ± 0.1	NA	2.4 ± 0.2
CorA[h]	3.8 ± 0.2	4.5 ± 0.3	NT[i]	3.6 ± 0.2	NT	NT

[a] L1210 (ATCC CCL 219)—mouse lymphocytic leukemia cells.
[b] HL-60 (ATCC CCL 240)—human promyelocytic leukemia cells.
[c] HeLa S3 (ATCC CCL 2.2)—human epithelial carcinoma cells.
[d] CCRF-CEM (ATCC CCL 219)—human leukemic T-cell lymphoblasts.
[e] HT-29 (ATCC HTB 38)—human colon adenocarcinoma cells.
[f] Colo 201 (ECACC 87091201)—human colon adenocarcinoma cells.
[g] NA = not active at 10 μmol/L.
[h] Coruscanone A.
[i] NT = not tested.

In summary, we have described reproducible conditions for the Knoevenagel condensation of cyclopent-4-ene-1,3-dione with a variety of aromatic and unsaturated aldehydes, and prepared a series of desmethoxy analogues of the antifungal natural product, coruscanone A. Evaluation of antifungal activity showed that some of the compounds retained antifungal effect on the level of the natural product. Similar to previously described derivatives of coruscanone A, further substitution of the phenyl or styryl moiety as well as switch from phenyl to a naphthyl or heterocyclic ring led to a decrease or complete loss of the biological effect. The most active compound **2f** was comparable to fluconazole as the drug standard against *C. albicans*, *C. tropicalis* and *C. lusitaniae*, and was superior to the drug against *C. parapsilosis*, *C. krusei*, and *C. glabrata*. Even though Michael addition could be the reason for the binding of the compound to its cellular target, it is notable that further screening experiments indicated reduced cytotoxicity of the compound in comparison to coruscanone A.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.08.059.

References and notes

1. (a) Sheng, C.; Zhang, W. *Curr. Med. Chem.* **2011**, *18*, 733; (b) Ostrosky-Zeichner, L.; Casadevall, A.; Galgiani, J. N.; Odds, F. C.; Rex, J. H. *Nat. Rev. Drug Discovery* **2010**, *9*, 719.
2. (a) Pasqualotto, A. C.; Thiele, K. O.; Goldani, L. Z. *Curr. Opin. Investig. D* **2010**, *11*, 165; (b) Chai, X.; Zhang, J.; Cao, Y.; Zou, Y.; Wu, Q.; Zhang, D.; Jiang, Y.; Sun, Q. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 686.
3. Di Santo, R. *Nat. Prod. Rep.* **2010**, *27*, 1084.
4. Cho, Y. S.; Wu, K.-D.; Moore, M. A.; Chou, T.-C.; Danishefsky, S. J. *Drugs Fut.* **2005**, *30*, 737.
5. Šenel, P.; Tichotová, L.; Votruba, I.; Buchta, V.; Špulák, M.; Kuneš, J.; Nobilis, M.; Krenk, O.; Pour, M. *Bioorg. Med. Chem.* **2010**, *18*, 1988.
6. Li, X.-C.; Ferreira, D.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; ElSohly, H. N.; Nagle, D. G.; Smillie, T. J.; Khan, I. A.; Walker, L. A.; Clark, A. M. *J. Am. Chem. Soc.* **2004**, *126*, 6872.
7. Babu, K. S.; Li, X.-C.; Jacob, M. R.; Zhang, Q.; Khan, S. I.; Ferreira, D.; Clark, A. M. *J. Med. Chem.* **2006**, *49*, 7877.
8. For other work on coruscanone A and analogues, see: (a) Shestak, O. P.; Novikov, V. L.; Martyyas, E. A.; Anisimov, M. M. *Pharm. Chem. J.* **2009**, *43*, 498; (b) Shestak, O. P.; Novikov, V. L. *Russ. Chem. Bull.* **2010**, *59*, 81.
9. DePuy, C. H.; Wells, P. R. *J. Am. Chem. Soc.* **1960**, *82*, 2909.
10. Aoyama, Y.; Konoike, T.; Kanda, A.; Naya, N.; Nakajima, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1695.
11. Bartoli, G.; Beleggia, R.; Giuli, S.; Giuliani, A.; Marcantoni, E.; Massaccesi, M.; Paletti, M. *Tetrahedron Lett.* **2006**, *47*, 6501.
12. Kantevari, S.; Bantu, R.; Nagarapu, L. *J. Mol. Catal. A: Chem.* **2007**, *269*, 53.
13. (a) Lehnert, W. *Tetrahedron* **1974**, *30*, 301; (b) Green, B.; Crane, R. I.; Khaidem, I. S.; Leignton, R. S.; Newaz, S. S.; Smyser, T. E. *J. Org. Chem.* **1985**, *50*, 640.
14. Shanthan, R.; Venkataratnam, R. V. *Tetrahedron Lett.* **1991**, *32*, 5821.
15. Yadav, J. S.; Bhunia, D. C.; Singh, V. K.; Srihari, P. *Tetrahedron Lett.* **2009**, *50*, 2470.
16. Berrué, F.; Antoniotti, S.; Thomas, O. P.; Amade, P. *Eur. J. Org. Chem.* **2007**, 1743.
17. Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777.
18. (a) Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi. Approved standard. Document M38-A2. Clinical Laboratory Standard Institute, Wayne, PA, 2008; (b) Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. Approved standard. Document M27-A3. Clinical Laboratory Standard Institute, Wayne, PA, 2008.
19. Hocek, M.; Holý, A.; Votruba, I.; Dvořáková, H. *J. Med. Chem.* **2000**, *43*, 1817.
20. Carmichael, J.; DeGraff, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. *Cancer Res.* **1987**, *47*, 936.
21. Abassi, Y. A.; Xi, B.; Zhang, W.; Ye, P.; Kirstein, S. L.; Gaylord, M. R.; Feinstein, S. C.; Wang, X.; Xu, X. *Chem. Biol.* **2009**, *16*, 712.