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A new strategy for accessing (*S*)-1-(furan-2-yl)pent-4-en-1-ol: a key precursor of Ipomoeassin family of compounds and C1–C15 domain of halichondrins

Subba Rao Jammula [a,b], Venkateswara Rao Anna [b], Sudhakar Tatina [a], Thalishetti Krishna [a], B. Yogi Sreenivas [c], Manojit Pal [c,*]

[a] Custom Pharmaceutical Services, Dr. Reddys Laboratories Limited, Bollaram Road, Miyapur, Hyderabad 500 049, India
[b] Department of Chemistry, Koneru Lakshmaiah University (KLU), Green Fields, Vaddeswaram, Guntur District, Andhra Pradesh 522502, India
[c] Dr Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India

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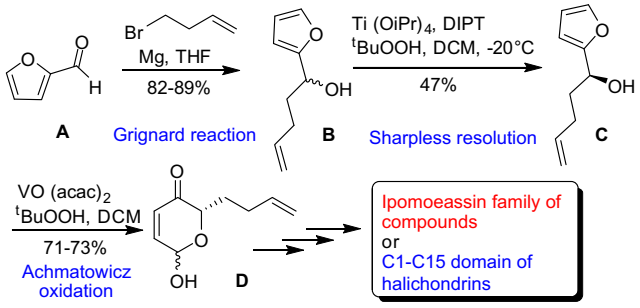
ABSTRACT

A highly efficient synthesis of (*S*)-1-(furan-2-yl)pent-4-en-1-ol, known to be an initial precursor of Ipomoeassin family of compounds and C1–C15 domain of halichondrins has been achieved via a sequence involving the use of Weinreb amide formation followed by Weinreb ketone synthesis and finally CBS (Corey–Bakshi–Shibata) reduction. Detailed study on improvement of each step is described. The title compound was converted to a potential cytotoxic agent for further pharmacological studies.

Ipomoeassin family of resin glycosides isolated from the morning glory *Ipomoea squamosa* (collected from the Suriname rain forest)[1,2] are known to posses interesting cytotoxic properties. Due to their unique structural features and cytotoxic activities synthesis of this class of compounds attracted particular attention.[3,4] The reported synthesis of some of the members of this family involved the preparation of an intermediate i.e. (*S*)-1-(furan-2-yl) pent-4-en-1-ol (**C**) from furan-2-carbaldehyde (**A**) via **B** leading to the key precursor **D** (Scheme 1).[3] Notably, the compound **C** has also been explored for the synthesis of C1–C15 domain of halichondrins[5] (a class of polyether macrolides isolated from the marine sponge *Halichondria okadai* that showed unusual antitumor activities) and palmerolide A[6] (a 20-membered macrocyclic polyketide that showed potent and selective cytotoxicity activities). While the sequence shown in Scheme 1 is an useful method for the preparation of **C** the methodology especially the second step (Sharpless resolution) however suffers from some limitations such as isolation of desired enantiomer **C** in moderate yield (~47%), and requirement of low temperature (−20 °C).[3–5] Thus there was a need for the development of alternative and high yielding method for the preparation of **C**. This prompted us to adopt a different



Scheme 1. Reported synthesis of intermediate **C**[3] and its further uses.

strategy for accessing **C** from furan-2-carboxylic acid (**E**) which is based on the use of Weinreb amide formation as a key step followed by Weinreb ketone synthesis and finally CBS (Corey–Bakshi–Shibataa) reduction (Scheme 2). We were particularly interested in avoiding the resolution step of previously reported method that decreased the yield of desired stereoisomer significantly. Herein we report our results and potential of this strategy that includes assessing the generality and scope of each step involved. To the best of our knowledge exploration of a same or similar approach for accessing **C** has not been reported earlier.

* Corresponding author. Tel.: +91 40 6657 1500; fax: +91 40 6657 1581.
E-mail address: manojitpal@rediffmail.com (M. Pal).

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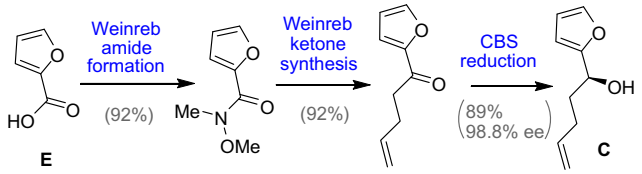
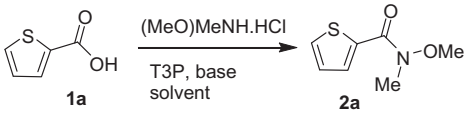


Scheme 2. An alternative strategy for the synthesis of **C** (figure in the parentheses represents isolated yield of respective product after performing the actual reaction, see infra for details).

Since the formation of a Weinreb amide was the first step of our pre-designed approach (Scheme 2) hence establishing a suitable and efficient condition for this amide formation was the key challenge initially. Weinreb amides[7] are well known precursors for a range of compounds including carbonyl derivatives, alkynes, heterocycles, natural products etc. Generally, these amides are prepared via the treatment of *N,O*-dimethylhydroxylamine with an activated carboxylic acid derivative. A variety of peptide coupling reagents has been used for this purpose that includes BOP,[8] DCC,[9] DCC/HOBt,[10] CBr_4/PPh_3,[11] EDC/HOBt,[12] and CDMT.[13] However, a recent report on the use of commercially available T3P (1-propanephosphonic acid cyclic anhydride) and DBU to obtain Weinreb amides[14] prompted us to adopt a similar strategy in our case. While this methodology mainly focused on the use of N^{α}-protected amino/peptide acids only we anticipated that the conditions used in these reactions might be effective for other classes of acids too. Moreover, the use of T3P has several advantages including milder reaction conditions, wide functional group tolerance, high product yields, and less toxicity. Formation of water soluble byproducts and their easy separation from the main products is another advantage associated with the use of T3P. Nevertheless, we performed an optimization study to establish the best reaction condition suitable for the preparation of Weinreb amides from non-amino/peptide acids. Accordingly, the reaction of thiophene-2-carboxylic acid (**1a**) with *N,O*-dimethylhydroxylamine hydrochloride in the presence of T3P was performed under various conditions and results are summarized in Table 1. A number of bases e.g. Et_3N (triethylamine), DIPEA, and DBU were examined in this reaction. For each base at least four solvents e.g. THF, EtOAc, MeCN, and toluene were tested. It is evident from Table 1 that Et_3N was better than other bases when used in THF (Entry 5, Table 1). Moreover, being cheaper than DBU (that was used in the previously reported method)[14] the use of Et_3N is advantageous. Additionally, in contrast to earlier method the amine was used directly as its hydrochloride salt in the present case. While the duration of the reaction was 60 min the decrease in reaction time decreased the yield of **2a** (Entry 6, Table 1). Overall, the condition of Entry 5 of Table 1 was identified as the best one and used for further study.

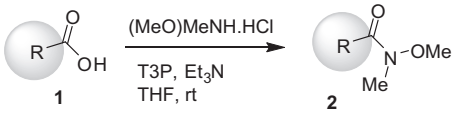
Table 1
Effect of reaction conditions on formation of Weinreb amide **2a**[a]

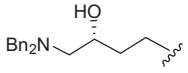
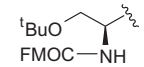
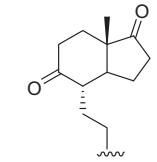
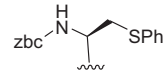


Entry	Catalyst	Solvent	Temp (°C)/Time (min)	Yield (%)[b]
1	DIPEA	THF	120	68
2	DIPEA	EtOAc	120	70
3	DIPEA	CH_3CN	120	70
4	DIPEA	Toluene	120	28
5	Et_3N	THF	60	96
6	Et_3N	THF	40	73
7	Et_3N	EtOAc	60	82
8	Et_3N	CH_3CN	60	86
9	DBU	THF	65	90
10	DBU	EtOAc	70	78
11	DBU	CH_3CN	70	84

[a] The reaction was performed by using **1a** (8.9 mmol), (MeO)MeNH.HCl (13.3 mmol), T3P (50% in EtOAc, 10.6 mL, 17.7 mmol), and a base (22.2 mmol) in a solvent (15 mL) at room temp (25 °C) under nitrogen.
[b] Isolated yield.

Table 2
Synthesis of Weinreb amides (**2**) in the presence of T3P and triethylamine[a]

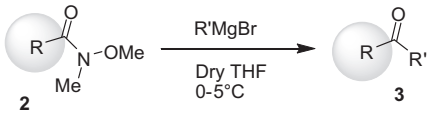


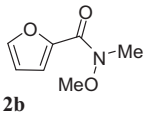
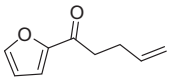
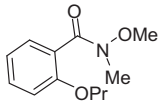
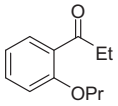
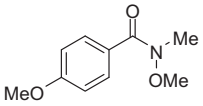
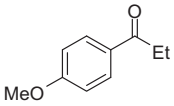
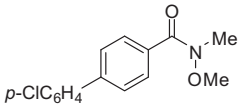
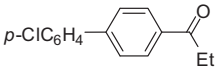
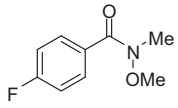
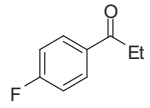
Entry	Carboxylic acid (**1**); R=	Product (**2**)	Time (min)	Yield[b] (%)
1	**1a**; 2-Thienyl	**2a**	60	96
2	**1b**; Furan-2-yl	**2b**	80	92
3	**1c**; *p*-$ClCH_2C_6H_4$	**2c**	60	90
4	**1d**; *o*-IC_6H_4	**2d**	120	84
5	**1e**; *p*-NO_2(*o*-Cl)C_6H_3	**2e**	60	84
6	**1f**; *o*-$MeCOC_6H_4$	**2f**	120	86
7	**1g**; Ph	**2g**	120	98
8	**1h**; *o*-$PrOC_6H_4$	**2h**	110	90
9	**1i**; Tetrahydrofuran-2-yl	**2i**	60	86
10	**1j**; PhCH = CH-	**2j**	90	87
11	**1k**; *p*-$MeOC_6H_4$	**2k**	60	92
12	**1l**; *p*-(*p*-ClC_6H_4)C_6H_4	**2l**	70	92
13	**1m**; *p*-FC_6H_4	**2m**	80	92
14	**1n**; Cyclohex-3-enyl	**2n**	110	80
15	**1o**; 	**2o**	60	92
16	**1p**; 	**2p**	240	89
17	**1q**; 	**2q**	180	88
18	**1r**; 	**2r**	120	86

[a] The reaction was performed by using **1** (8.9 mmol), (MeO)MeNH.HCl (13.3 mmol), T3P (50% in EtOAc, 10.6 mL, 17.7 mmol), and Et_3N (22.2 mmol) in THF (15 mL) at room temp (25 °C) under nitrogen.
[b] Isolated yield.

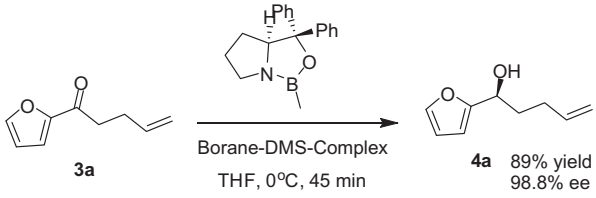
To examine the applicability of this methodology to other non-amino/peptide acids a wide range of carboxylic acids were employed under the optimized reaction conditions (Table 2, see ESI). These acids may carry a group like heteroaryl (entry 1 and 2, Table 2), aryl (entries 3–8 and 11–13, Table 2), cycloalkyl (entry 14 and 17, Table 2), alkenyl (entry 10, Table 2), or cyclic ether moiety (entry 9, Table 2). Indeed, appropriately protected amino acids were also employed in this reaction (entry 15, 16, and 18, Table 2). The reaction proceeded well in all these cases affording desired Weinreb amides (**2**) in good to high yields. All the amides synthesized were characterized by spectral (NMR, IR, and HRMS) data. For example, an IR absorption at 1621 cm^{-1} and a ^{13}C NMR signal at 162.2 ppm observed in case of compound **2a** indicated the presence of an amidic carbonyl group. Moreover two singlets appeared at δ 3.78 and 3.37 in the ^{1}HNMR spectra and at 61.5 and 33.0 ppm in the ^{13}CNMR spectra of the same compound were due to the -OMe and -NMe groups, respectively.

Table 3
Preparation of ketones (**3**) via Weinreb ketone synthesis using amides **2b**, **2h**, **2k**, **2l**, and **2m**[a]



Entry	Amide (**2**)	Ketone (**3**)	Time (min)	Yield[b] (%)
1	 **2b**	 **3a**	80	92[c]
2	 **2h**	 **3b**	120	76[d]
3	 **2k**	 **3c**	60	89[d]
4	 **2l**	 **3d**	75	88[d]
5	 **2m**	 **3e**	80	94[d]

[a] Reactions were performed using amide **2** (3.3 mmol), alkyl magnesium bromide (1.0 M in THF, 9.8 mL, 10 mmol), in dry THF (10 mL) under argon atmosphere at 0–5 °C.
[b] Isolated yield.
[c] But-3-enyl magnesium bromide was used as the Grignard reagent.
[d] Ethyl magnesium bromide was used as the Grignard reagent.

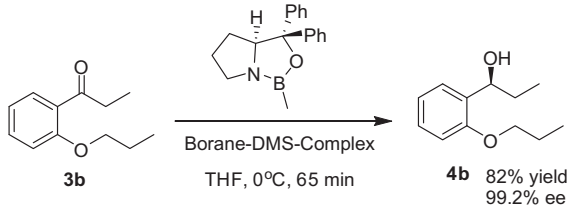


Scheme 3. Reduction of **3a** under CBS reduction conditions.

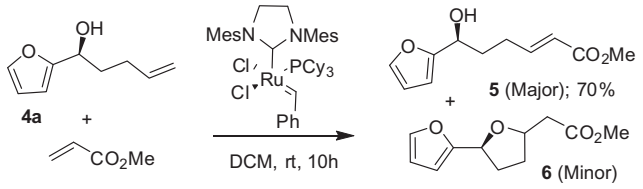
To follow our strategy (Scheme 2) and expand the further synthetic potential of the present Weinreb amide synthesis we performed Weinreb ketone synthesis[7a,15] using selected amides including **2b** (Table 3). Thus amide **2b** was treated with but-3-enyl magnesium bromide (a Grignard reagent) when the desired ketone **3a** was isolated in excellent yield (entry 1, Table 3). Similarly amides **2h**, **2k**, **2l**, and **2m** were treated with ethyl magnesium bromide individually under the same reaction conditions. The reaction proceeded well to afford the corresponding ketone (**3b**–**e**) in good to high yield (entries 2–5, Table 3).[16] The spectral data of all these compounds e.g. an IR absorption in the range 1655–1675 cm^{-1} and a ^{13}C signal in the range 175–200 cm^{-1} confirmed the presence of a ketone carbonyl group. Moreover, the disappearance of signals for -NMe and -OMe group of amide moiety in the ^{1}H and ^{13}C NMR spectra clearly indicated chemical transformation of –CONMeOMe moiety during the reaction. Nevertheless, we were delighted with these results and therefore decided to focus on the next step of our strategy (Scheme 2). Accordingly, the ketone **3a** and **3b** were reduced to the corresponding alcohol **4a** and **4b** respectively under the condition of CBS (Corey–Bakshi–Shibataa) reduction[17] (Schemes 3 and 4). In general the alcohols were obtained in high yields with good enantiomeric excess (ee > 98%) as indicated by results of chiral HPLC. The specific optical rotation (SOR $[\alpha]_D^{20} = -6.6°$, see ESI) of **4a** was found to be identical with the reported value.[3] Thus we were able to prepare **4a** avoiding the resolution step of previously reported method thereby improving the yield of desired stereoisomer [overall yield 75% (Scheme 2) vs ~42% of reported method (Scheme 1)].

Having prepared the compound **4a** (or **C**, Schemes 1 and 2) successfully following our new strategy we then performed the formal synthesis of compound **D** [(*S*)-2-(but-3-enyl)-6-hydroxy-2*H*-pyran-3(6*H*)-one, Scheme 1] using $VO(acac)_2$ (2 mol %) and *t*BuOOH in dichloromethane according to the reported procedure.[3,5] The **D** was isolated in 76% yield confirming that the strategy presented here could be an useful alternative toward the synthesis of Ipomoeassin family of compounds or construction of C1–C15 domain of the halichondrins.

Recently, 6-(furan-2-yl)-6-hydroperoxyhex-2-enoic acid framework has been explored as potential cytotoxic agents against three cancer cell lines e.g. MDA-MB-231 (breast), A-549 (lung), and HT29 (colon).[18] Prompted by this report we converted the compound **4a** to a structurally similar 6-(furan-2-yl)-6-hydroxyhex-2-enoic acid



Scheme 4. Reduction of **3b** under CBS reduction conditions.



Scheme 5. Preparation of compound **5** via Grubbs olefin metathesis.

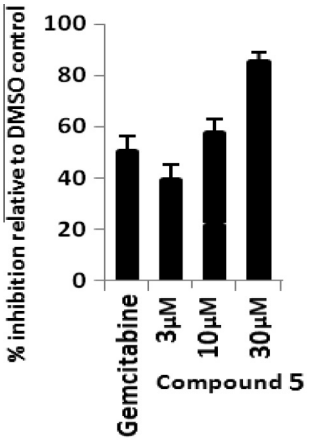


Figure 1. % inhibition of breast adenocarcinoma cells (MCF-7) after 72 h of compound treatment.

derivative (**5**) using the Grubbs olefin metathesis[19] as shown in Scheme 5. Thus the compound **4a** was treated with methyl acrylate in the presence of Grubbs catalysts (second generation) in dichloromethane at room temperature when the desired product **5** was isolated in 70% yield. Notably, the compound **6** seemed to be formed due to the intermolecular cyclization of compound **5** was also isolated as a minor product in this reaction. We were delighted to isolate the product **5** as this compound not only may attract attention due to its potential pharmacological interest but also may serve as a precursor for other target compounds.

The compound **5** was tested at 3, 10, and 30 μM against the breast adenocarcinoma cells MCF-7 using the sulphorhodamine B (SRB) assay[20a,b] with gemcitabine[20c] (10 μM) as a reference compound. The compound **5** showed dose dependent inhibition (i.e. ~40, 60 and 90% at 3, 10 and 30 μM) of MCF-7 cells when gemcitabine showed ~50% inhibition at 10 μM (Fig. 1). Thus compound **5** deserves further attention as a potential anticancer agent. Nevertheless, synthesis of other analogues of compound **5** is currently underway upon completion of which all these compounds will be evaluated for their potential pharmacological activities.

In conclusion, a practical and efficient synthesis of (*S*)-1-(furan-2-yl)pent-4-en-1-ol has been achieved in 75% overall yield (better than ~42% overall yield of the previously reported method). The synthesis involved the use of Weinreb amide formation followed by Weinreb ketone synthesis and finally CBS (Corey–Bakshi–Shibataa) reduction of the resulting ketone. The methodology does not require resolution of enantiomers. To expand the generality and scope of each step involved a variety of Weinreb amides were prepared mostly from non-amino/peptide acids using the cheaper and improved optimized conditions. Some of these amides were converted to the corresponding ketones two of which were taken forward for CBS reduction. The furan precursor synthesized was converted to the next intermediate i.e. (*S*)-2-(but-3-enyl)-6-hydroxy-2*H*-pyran-3(6*H*)-one and a 6-(furan-2-yl)-6-hydroxyhex-2-enoic acid derivative of potential pharmacological interest. Overall, the current methodology not only presents a better alternative toward the synthesis of Ipomoeassin family of compounds or construction of C1–C15 domain of halichondrins but also may find applications in synthesizing small molecules for Chemical Biology/Med Chem purpose.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.07.059.

References and notes

1. Cao, S.; Guza, R. C.; Wisse, J. H.; Miller, J. S.; Evans, R.; Kingston, D. G. I. *J. Nat. Prod.* **2005**, *68*, 487.
2. Cao, S.; Norris, A.; Wisse, J. H.; Miller, J. S.; Evans, R.; Kingston, D. G. I. *Nat. Prod. Res.* **2007**, *21*, 872.
3. Nagano, T.; Pospíšil, J.; Chollet, G.; Schulthoff, S.; Hickmann, V.; Moulin, E.; Herrmann, J.; Müller, R.; Fürstner, A. *Chem. Eur. J.* **2009**, *15*, 9697.
4. Fürstner, A.; Nagano, T. *J. Am. Chem. Soc.* **2007**, *129*, 1906.
5. Jackson, K. L.; Henderson, J. A.; Morris, J. C.; Motoyoshi, H.; Phillips, A. J. *Tetrahedron Lett.* **2008**, *49*, 2939.
6. Prasad, K. R.; Pawar, A. B. *Org. Lett.* **2011**, *13*, 4252.
7. (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815; (b) Sivaraman, B.; Aidhen, I. S. *Synthesis* **2008**, 3707; (c) Banwell, M.; Smith, J. *Synth. Commun.* **2011**, *2001*, 31; (d) Khlestkin, V. K.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967.
8. (a) Maugras, I.; Poncet, J.; Jouin, P. *Tetrahedron* **1990**, *46*, 2807; (b) Shreder, K.; Zhang, L.; Goodman, M. *Tetrahedron Lett.* **1998**, *39*, 221.
9. Braun, M.; Waldmuller, D. *Synthesis* **1989**, 856.
10. Dinh, T. Q.; Armstrong, R. W. *Tetrahedron Lett.* **1996**, *37*, 1161.
11. Einhorn, J.; Einhorn, C.; Luche, J. L. *Synth. Commun.* **1990**, *20*, 1105.
12. (a) Spaltenstein, A.; Leban, J. J.; Huang, J. J.; Reinhardt, K. R.; Viveros, O. H.; Sigafoos, J.; Crouch, R. *Tetrahedron Lett.* **1996**, *37*, 1343; (b) Pearson, C.; Rinehart, K. L.; Sugano, M. *Tetrahedron Lett.* **1999**, *40*, 411.
13. DeLuca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534.
14. Sharnabai, K. M.; Nagendra, G.; Vishwanatha, T. M.; Sureshbabu, V. V. *Tetrahedron Lett.* **2013**, *54*, 478.
15. For applications of Weinreb ketone synthesis, see: (a) Paek, S.-M.; Seo, S.-Y.; Kim, S.-H.; Jung, J.-W.; Lee, Y.-S.; Jung, J.-K.; Suh, Y.-G. *Org. Lett.* **2005**, *7*, 3159; (b) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2008**, *10*, 4489; (c) Shimizu, T.; Satoh, T.; Murakoshi, K.; Sodeoka, M. *Org. Lett.* **2005**, *7*, 5573.
16. It is necessary to add the amide **2** into the Grignard reagent (instead of vice versa) to obtain the best yield of ketone **3**.
17. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925; (c) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880.

18. Guerra, F. M.; Zubıa, E.; Ortega, M. J.; Moreno-Dorado, F. J.; Massanet, G. M. *Tetrahedron* **2010**, *66*, 157.
19. (a) Grubbs, R. H.; Trnka, T. M. Ruthenium-catalyzed olefin metathesis. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, FRG, 2004. doi: 10.1002/3527603832.ch6; (b) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.
20. (a) Rubinstein, L. V.; Shoemaker, R. H.; Paull, K. D.; Simon, R. M.; Tosini, S.; Skehan, P.; Scudiero, D. A.; Monks, A.; Boyd, M. R. *J. Natl Cancer Inst.* **1990**, *82*, 1113; (b) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl Cancer Inst.* **1990**, *82*, 1107; (c) Chu, E.; DeVita, V. T. *Physicians' Cancer Chemotherapy Drug Manual*; Jones & Bartlett, 2007.