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A new approach to fused furan ring systems and benzofurans: intramolecular cyclization reactions of unsaturated acyloxy sulfone derivatives

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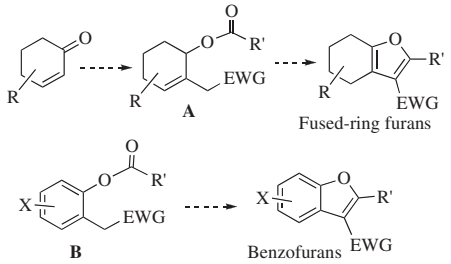
ABSTRACT

Unsaturated acyloxy sulfones **3** undergo intramolecular cyclization upon deprotonation with LHMDS in THF. Dehydration and double bond isomerization of the products upon exposure to acid, gave the fused ring furans, **4**, in good yields. This strategy could be readily adapted to prepare substituted benzofurans **12** from the cyclization reactions of acyloxy sulfones **11** prepared from phenols. Finally, this approach could be successfully modified to access dihydropyrans and benzopyrans.

Methods for the synthesis of fused furan ring systems have been of much interest over the years.[1] The interest in this area has been partly stimulated by the occurrence of a number of furanosesquiterpene natural products[2] having interesting structural skeletons such as pallescensin A, tubipofurane, and echinofuran. Attesting to this interest is a recent total synthesis of pallascensin A, in which the annulation of the furan ring to a functionalized decalone was accomplished by reaction of dichlorocarbene with the enol ether of the decalone followed by treatment of the dichlorocyclopropane intermediate with base.[3] Another route that was recently disclosed to fused furan ring systems used Au(III) to catalyze the cycloisomerization of 2-alkynylcycloalk-2-enols.[4]

The benzofuran scaffold has been identified as a 'privileged structure' in medicinal chemistry.[5] Members of this class of compounds have shown biological activities ranging from antifungal and antimicrobial to antagonists for the H_3 receptor and angiotensin II.[6] Hence the syntheses of benzofurans have received much greater attention and a number of different synthetic routes have been reported to access this class of molecules.[7] Recently, the synthesis of 3-alkenylbenzofurans has been achieved using tandem palladium catalyzed oxidative cyclization followed by Heck coupling with unsaturated carbonyl substrates.[8] Another approach involves intramolecular Wittig cyclization on a phenolic ester followed by elimination of triphenylphosphine oxide to give the benzofuran.[9] Recently, polycyclic fused benzofurans were prepared by a $TiCl_4$ mediated Baylis–Hillman reaction of aromatic cyclic 1,2-diones with cycloalkenones followed by cyclization of the intermediates with methanesulfonic acid.[10] An interesting solid phase synthesis that involves the intramolecular alkylation of an aryloxy sulfonyl carbanion on an epoxide to generate an intermediate that loses formaldehyde and sulfinate to generate 3-arylbenzofuran ring systems has been reported.[11] Another approach to substituted furans involves the deprotonation and subsequent reaction of a resin bound γ-methoxy allyl sulfone with aldehydes, followed by ring closure to the furan ring system accompanied by cleavage from the solid support upon treatment with acid.[12]

Given the importance and interest in the synthesis of fused furan ring systems, we thought that a general method to annulate furan ring systems onto readily accessible cycloalkenones would be a valuable method that would complement existing methodologies. The plan was to take advantage of some of our earlier work on the intramolecular cyclization reactions of γ and δ acyloxy sulfones which was used to prepare a variety of chiral nonracemic



Scheme 1.

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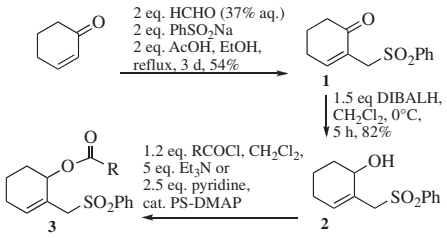


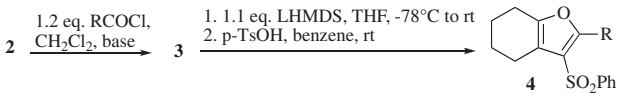
Scheme 2.

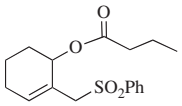
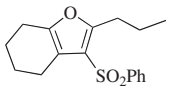
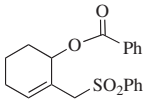
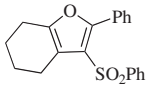
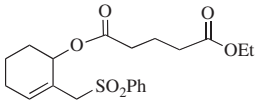
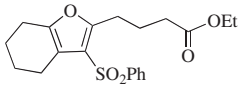
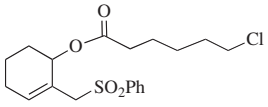
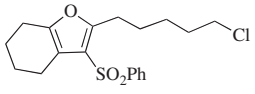
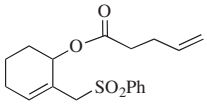
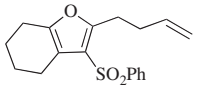
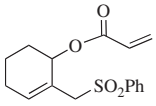
dihydrofurans/pyrans.[13] Our proposed synthetic approach to fused furan ring systems and benzofurans is shown in Scheme 1. In the key step, we hypothesized that the intramolecular cyclization of carbanions derived from substrates of the type A having a strong electron withdrawing moiety, would proceed to give a lactol that would dehydrate and isomerize to give the furan ring. We also hypothesized that similar chemistry with type B substrates would lead to a useful synthesis of benzofurans. In this publication, we report that acyloxy sulfones of the type A and B, undergo efficient intramolecular cyclization reactions and provide a new method for the preparation of functionalized fused furan ring systems and benzofurans.

We decided to demonstrate the viability of this annulation method using commercially available 2-cyclohexenone as the model starting material and a sulfone group as the EWG. The conversion of cyclohexenone to ketosulfone **1** by a two-step procedure that involves initial formation of a sulfide followed by its oxidation to sulfone [(i) benzenethiol, HCHO, Et_3N, EtOH, reflux, 5 d; (ii) oxone] has been reported.[14,15] However, we found that the desired ketosulfone **1** could be obtained directly in one step by treatment of 2-cyclohexen-1-one with 2 equiv each of formaldehyde (37% aqueous solution), sodium benzenesulfinate and acetic acid in ethanol at reflux for 3 days (Scheme 2). Acetic acid is a required reagent for the formation of the desired product. Subsequently, the reduction of **1** using DIBALH in dichloromethane at 0 °C, gave the unsaturated hydroxysulfone **2** in 82% yield after purification. A variety of acyloxy sulfones, **3**, were prepared in good yields by treating **2** with 1.2 equiv of the desired acid chloride in CH_2Cl_2 in the presence of triethylamine as base (Table 1). In some cases, the yields of the desired esters were low when triethyl amine was used as base. For those substrates, the yields were greatly improved by using pyridine as base in dichloromethane in the presence of a catalytic amount (12 mol %) of polystyrene supported-DMAP[16] in place of triethylamine.[17]

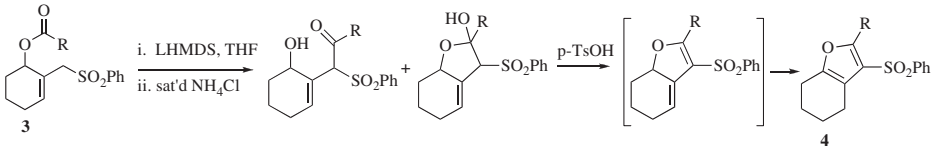
With the unsaturated acyloxy sulfones **3** in hand, their intramolecular cyclization reactions were examined. The sulfone **3a** was

Table 1
Synthesis of fused ring furans **4** via intramolecular cyclization of acyloxy sulfones **3**

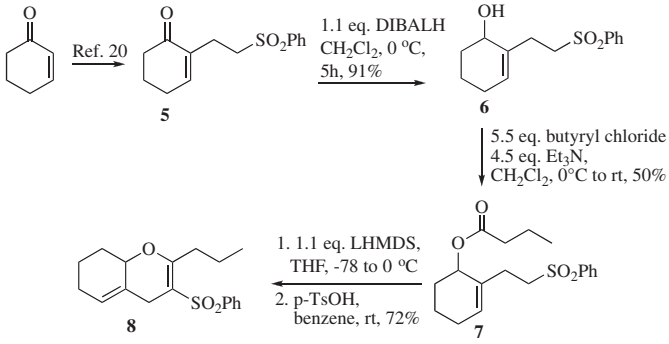


Entry	Acyl sulfone **3**	Yield (%)	Fused furan **4**	Yield (%)
1	 **3a**	62[a]	 **4a**	66
2	 **3b**	72[a]	 **4b**	70[c]
3	 **3c**	42[a] 88[b]	 **4c**	75
4	 **3d**	49[a] 80[b]	 **4d**	71
5	 **3e**	67[b]	 **4e**	89
6	 **3f**	69[a]		0

[a] 5.0 equiv Et_3N as base.
[b] 2.5 equiv pyridine as base and polymer supported-DMAP (0.12 equiv).
[c] Dehydration/isomerization step was carried out at 50 °C for 10 h.



Scheme 3.



Scheme 4.

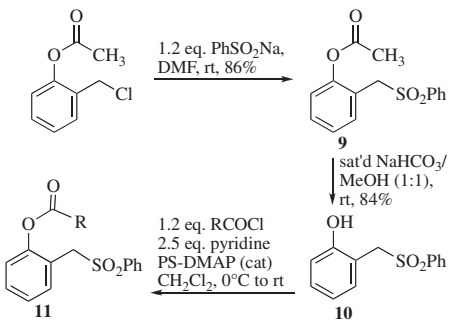
deprotonated with 1.1 equiv of LHMDS at −78 °C in THF. The reaction mixture was initially maintained at this temperature for 6 h and then subsequently at room temperature for 20 h. After work up, the desired products of the intramolecular cyclization, a diastereomeric mixture of lactols and the corresponding open-chain hydroxyketones (as evidenced by ^{1}H NMR and IR spectra), was isolated. When the crude reaction product was treated with a catalytic amount of *p*-TsOH in benzene for 16 h at room temperature, dehydration followed by isomerization occurred to give bicyclic furan **4a** in 66% yield after chromatographic purification (Table 1).[18] In the case of the benzoate **3b**, the intramolecular cyclization proceeded smoothly but it was necessary to heat the intermediate lactol/hydroxyketone mixture at 50 °C for 10 h to effect furan formation. The intramolecular cyclization was found to tolerate a variety of functionalized acyl groups (**3c**–**3e**) and in all cases the substituted fused furans were obtained in good yields. An exception was the sensitive acrylate derivative **3f** which did not undergo the desired cyclization under the standard conditions. Presumably, the starting material polymerized under the reaction conditions.

The generation of fused ring furans **4** could be rationalized by the pathway shown in Scheme 3. It is important to point out that the protons α to the sulfone are of comparable acidity to those on the methylene adjacent to the carbonyl of the acyl moiety. Formation of the carbanion α to the sulfone followed by its reaction with the acyl group gives a mixture of lactol and hydroxyketone products after work-up.[13] Treatment of the lactol/hydroxyketone mixture with a catalytic amount of *p*-TsOH leads to the dehydration of the lactol and isomerization of double bond, to give the more stable furan ring.

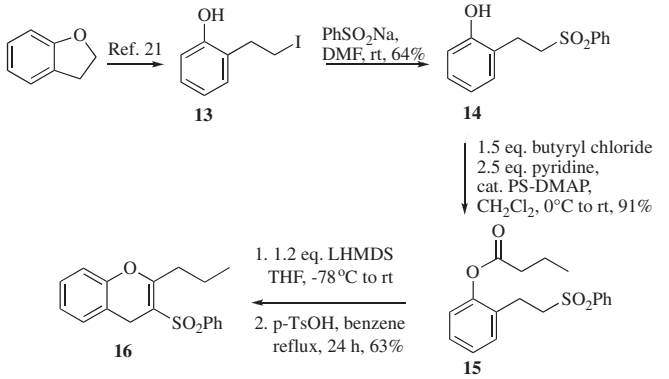
This methodology can easily be adapted to annulate pyran rings onto cycloalkenones. The sulfone **5**[19] was prepared following a literature procedure that involves a Baylis–Hillman reaction with vinyl sulfone.[20] The ketosulfone **5** was reduced by treatment with DIBALH to the unsaturated hydroxysulfone **6** (Scheme 4), which was then converted to the butanoyl derivative **7**. Treatment of unsaturated sulfone **7**, with LHMDS using standard conditions followed by dehydration of the intermediate product gave the dihydropyran product **8** in 72% yield after chromatographic purification. The presence of the isolated double bond in the cyclohexane ring of **8** is a useful handle for further synthetic manipulation in this class of intermediates.

Having successfully demonstrated the usefulness of our methodology for the synthesis of fused furans, its adaptation to the preparation of benzofurans was very appealing. The first goal was to develop a convenient synthetic route to the phenol **10** which could be converted to the acyloxy sulfones required for this study (Scheme 5). Commercially available 2-(chloromethyl)-phenyl acetate was treated with sodium benzenesulfinate in DMF at room temperature to give the corresponding sulfone **9** in 86% yield after chromatographic purification. In order to obtain the other acyl derivatives, the acetate **9**, was hydrolyzed using a 1:1 mixture of saturated sodium bicarbonate/methanol to give phenol **10**. The acyloxy sulfones **11**, were prepared by treatment of phenol **10** with the desired acid chloride in the presence of pyridine and catalytic polystyrene-DMAP in dichloromethane (Table 2).

The intramolecular cyclization reaction of sulfone **9** was first examined (Table 2). Treatment of **9** with 1.5 equiv of LHMDS in THF at −78 °C resulted in cyclization to give a mixture of the corresponding lactol/ketophenol as the products. The crude product was treated with catalytic *p*-TsOH in refluxing benzene for 12 h to give benzofuran **12a** in 96% yield after purification. In contrast to the synthesis of fused ring furans **4**, the dehydration did not proceed at room temperature and required harsher conditions. The results of the cyclization of substrates **11b**–**11d** (Table 2) clearly

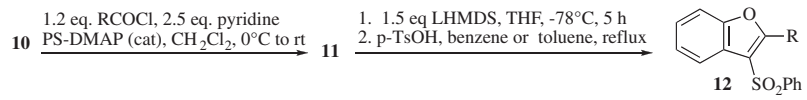


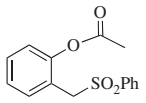
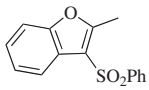
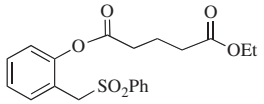
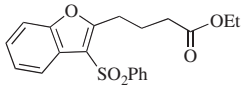
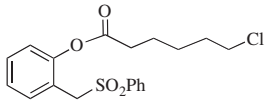
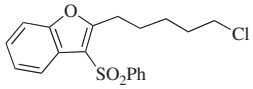
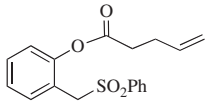
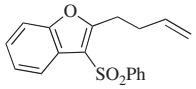
Scheme 5.



Scheme 6.

Table 2
Synthesis of substituted benzofurans **12**



Entry	Acyloxy sulfone	Yield (%)	Benzofuran **12**	Yield (%)
1	 **9**	–	 **12a**	96[a]
2	 **11b**	73	 **12b**	68[b]
3	 **11c**	87	 **12c**	63[c]
4	 **11d**	77	 **12d**	84[c]

[a] Benzene, reflux, 12 h.
[b] Benzene, reflux, 48 h.
[c] Toluene, reflux, 16 h.

demonstrate the broad application of this method to prepare substituted benzofurans.

We also examined the extension of this methodology to the synthesis of benzopyrans. Iodophenol **13** was prepared from 2,3-dihydrobenzofuran by a known procedure (Scheme 6).[21] The requisite sulfone **14** was prepared by reaction of iodide **13**, with sodium benzenesulfinate in DMF. Treatment of **14** with butyryl chloride using conditions described earlier gave acyloxy sulfone **15** in 91% yield. Sulfone **15** was treated with 1.2 equiv of LHMDS in THF to give a mixture of products that upon dehydration with *p*-TsOH in benzene at reflux gave the benzopyran **16** in 63% overall yield for two steps.

The first goal of this project was to develop a new methodology for the annulation of furans to cycloalkenones. The intramolecular cyclization reactions of acyloxy sulfones **3** to give fused ring furans **4** clearly established the viability of the proposed route. Using analogous chemistry, we were able to extend the application of this strategy to make substituted benzofurans, a class of compounds known for their biological activities. The extension of this chemistry to prepare dihydropyrans and benzopyrans further enhances the value of this study. It is now important to expand the scope of this furan annulation methodology to other cycloalkenones. It is also of interest to study the cyclization chemistry of substrates A and B (Scheme 1), which have electron withdrawing groups other than the sulfonyl moiety. This will broaden the diversity of products that one can obtain using this chemistry.

Acknowledgments

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References and notes

1. For reviews on the synthesis of furanosesquiterpenes see: (a) Fraga, B. M. *Nat. Prod. Rep.* **2005**, *22*, 465–486; (b) Allen, A. J.; Vaillancourt, V.; Albizati, K. F. *Org. Prep. Proced. Int.* **1994**, *26*, 1–84.
2. Saito, Y.; Hattori, M.; Iwamoto, Y.; Takashima, Y.; Mihara, K.; Sasaki, Y.; Fujiwara, M.; Sakaoku, M.; Shimizu, A.; Chao, X.; Kuroda, C.; Gong, X.; Hanai, R.; Tori, M. *Tetrahedron* **2011**, *67*, 2220–2231.
3. Foot, J. S.; Phillis, A. T.; Sharp, P. P.; Willis, A. C.; Banwell, M. G. *Tetrahedron Lett.* **2006**, *47*, 6817–6820.
4. Praveen, C.; Kiruthiga, P.; Perumal, P. T. *Synlett* **2009**, 1990–1996.
5. (a) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473–493; (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
6. (a) Lu, Z.; Ott, G. R.; Anand, R.; Liu, R.-Q.; Covington, M. B.; Vaddi, K.; Qian, M.; Newton, R. C.; Christ, D. D.; Trzaskos, J.; Duan, J. J.-W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1958–1962; (b) Hu, Y.; Xiang, J. S.; DiGrandi, M. J.; Du, X.; Ipek, M.; Laakso, L. M.; Li, J.; Li, W.; Rush, T. S.; Schmid, J.; Skotnicki, J. S.; Tam, S.; Thomason, J. R.; Wang, Q.; Levin, J. I. *Bioorg. Med. Chem.* **2005**, *13*, 6629–6644; (c) Gfesser, G. A.; Faghih, R.; Bennani, Y. L.; Curtis, M. P.; Esbenshade, T. A.; Hancock, A. A.; Cowart, M. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2559–2563; (d) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796–4805; (e) Cowart, M.; Pratt, J. K.; Stewart, A. O.; Bennani, Y. L.; Esbenshade, T. A.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 689–693; (f) Kawasaki, K.; Masabuchi, M.; Morikami, K.; Sogabe, S.; Aoyama, T.; Ebiike, H.; Niizuma, S.; Hayase, M.; Fujii, T.; Sakata, K.; Shindoh, H.; Shiratori, Y.; Aoki, Y.; Ohtsuka, T.; Shimma, N. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 87–91; (g) Bettinetti, L.; Schlotter, K.; Hübner, H.; Gmeiner, P. *J. Med. Chem.* **2002**, *45*, 4594–4597; (h) Halabalaki, M.; Aligiannis, N.; Papoutsi, Z.; Mitakou, S.; Moutsatsou, P.; Sekeris, C.; Skaltsounis, A.-L. *J. Nat. Prod.* **2000**, *63*, 1672–1674.
7. For recent reviews on the synthesis of benzofurans see: (a) De Luca, L.; Nieddu, G.; Porcheddu, A.; Giacomelli, G. *Curr. Med. Chem.* **2009**, *16*, 1–20; (b) Miyata, O.; Takeda, N.; Naito, T. *Heterocycles* **2009**, *78*, 843–871; (c) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog.Heterocycl. Chem.* **2009**, *21*, 179–223; (d) Katritzky, A. A.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613–5615.
8. Martínez, C.; Álvarez, R.; Aurrecoechea, J. M. *Org Lett.* **2009**, *11*, 1083–1086.
9. (a) Rao, M. L.; Awasthi, D. K.; Banerjee, D. *Tetrahedron Lett.* **2010**, *51*, 1979–1981; (b) De Luca, L.; Giacomelli, G.; Nieddu, G. *J. Org. Chem.* **2007**, *72*, 3955–3957; (c) Hercouet, A.; LeCorre, M. *Tetrahedron* **1981**, *37*, 2867–2873.
10. Basavaiah, D.; Roy, S.; Das, U. *Tetrahedron* **2010**, *66*, 5612–5622.
11. Nicolaou, K. C.; Snyder, S. A.; Bigot, A.; Pfefferkorn, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1093–1096.

12. Arvanitis, E. A.; Craig, D.; Timm, A. P. *ARKIVOC* **2002**, 19–27.
13. Jacobs, H. K.; Gopalan, A. S. *J. Org. Chem.* **1994**, *59*, 2014.
14. Cohen, T.; Kosarych, Z.; Suzuki, K.; Xu, L. *J. Org. Chem.* **1985**, *50*, 2965–2968.
15. Tamura, R.; Katayama, H.; Watabe, K.; Suzuki, H. *Tetrahedron* **1990**, *46*, 7757–7768.
16. PS-DMAP: 4% cross-linked poly(styrene-co-divinylbenzene) 1.5 mmol/g from Biotage.
17. All of the compounds prepared in this paper were characterized by IR, ^{1}H and ^{13}C NMR and elemental analysis.
18. *3-Benzenesulfonyl-2-propyl-4,5,6,7-tetrahydrobenzofuran* (**4a**). A solution of LHMDS (1 M in THF, 0.62 mL, 0.62 mmol) was added dropwise to a solution of **3a** (0.182 g, 0.57 mmol) in THF (10 mL) at −78 °C under N_2 and the reaction mixture was stirred at −78 °C for 6 h and then at rt for 20 h. The reaction was quenched with saturated 10% acetic acid solution (5 mL) and the THF was removed in vacuo. The residue was dissolved in EtOAc (50 mL), washed with brine (10 mL), dried (Na_2SO_4) and the solvent removed in vacuo. The crude lactol/ketosulfone mixture was dissolved in benzene (5 mL) and a catalytic amount of *p*-TsOH was added to the solution. The reaction was stirred at rt for 8 h. The reaction mixture was diluted with EtOAc (50 mL), washed with $NaHCO_3$ (3 × 10 mL), dried (Na_2SO_4) and the solvent removed in vacuo. The crude product was purified by radial chromatography (20% EtOAc in hexane) to give **4a** (0.113 g, 65.7%) as a white solid; mp 79–80 °C; IR (KBr) 2927, 2867, 1559 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03−7.79 m, 2H), 7.67–7.40 (m, 3H), 2.99 (t, *J* = 7.3 Hz, 2H), 2.58–2.29 (m, 4H), 1.87–1.15 (m, 6H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 150.4, 143.3, 133.0, 129.3, 127.0, 121.0, 115.9, 29.1, 23.0, 22.6, 22.5, 22.0, 21.2, 14.1; Anal. Calcd for $C_{17}H_{20}SO_3$: C, 67.08; H, 6.62. Found: C, 66.92; H, 6.86.
19. Hwu, J. R.; Hakimelahi, G. H.; Chou, C. *Tetrahedron Lett.* **1992**, *33*, 6469–6472.
20. Wang, W.; Yu, M. *Tetrahedron Lett.* **2004**, *45*, 7141–7143.
21. Zewge, D.; King, A.; Weissman, S.; Tschaen, D. *Tetrahedron Lett.* **2004**, *45*, 3729–3732.