Pergamon

Tetrahedron Letters 43 (2002) 1161–1164

TETRAHEDRON LETTERS

A general synthesis of dioxolenone prodrug moieties

Chong-Qing Sun,* Peter T. W. Cheng,* Jay Stevenson, Tamara Dejneka, Baerbel Brown, Tammy C. Wang, Jeffrey A. Robl and Michael A. Poss

Bristol-Myers Squibb Pharmaceutical Research Institute, PO Box 5400, Princeton, NJ 08543-5400, USA

Received 21 November 2001; revised 7 December 2001; accepted 14 December 2001

Abstract—A general method for the synthesis of dioxolenone prodrug moieties from appropriately substituted β-ketoesters is described. This novel and versatile sequence allows for the synthesis of alkyl- or aryl-substituted dioxolenone alcohols **8** or bromides **9**. Coupling of the bromides **9** to prepare bis-dioxolenone phosphonate prodrug esters is also presented.

Esters are the most commonly employed prodrug moieties for acid-derived drugs (e.g. carboxylate, phosphonate and phosphinate) due to the ubiquitous distribution of esterases in the blood, liver and other organs and tissues.[1] However, simple aliphatic or aromatic esters are often insufficiently labile in vivo (due primarily to the resulting steric hindrance at the acid functionality) to ensure the desired rate and extent of prodrug conversion to drug. This limitation can be overcome by the use of double esters such as (acyloxy)alkyl esters[2] in which the terminal ester moiety is more sterically accessible to esterases, as illustrated in Fig. 1 for phosphonic acids. Although the double ester prodrug approach has been widely used in solving delivery problems for drugs with poor absorption (notably in the case of fosinopril[3]), two significant problems are encountered using this type of prodrug. First, synthetic complications are introduced since a new asymmetric center is generated in the case where $R' \neq H$. This becomes especially problematic in the case of phosphonate bis(acyloxy)alkyl esters (where $R' \neq H$), which now contain multiple chiral centers both at phosphorus and on the prodrug moieties. Secondly, for the most simple case of (acyloxy)alkyl esters (where $R' =$

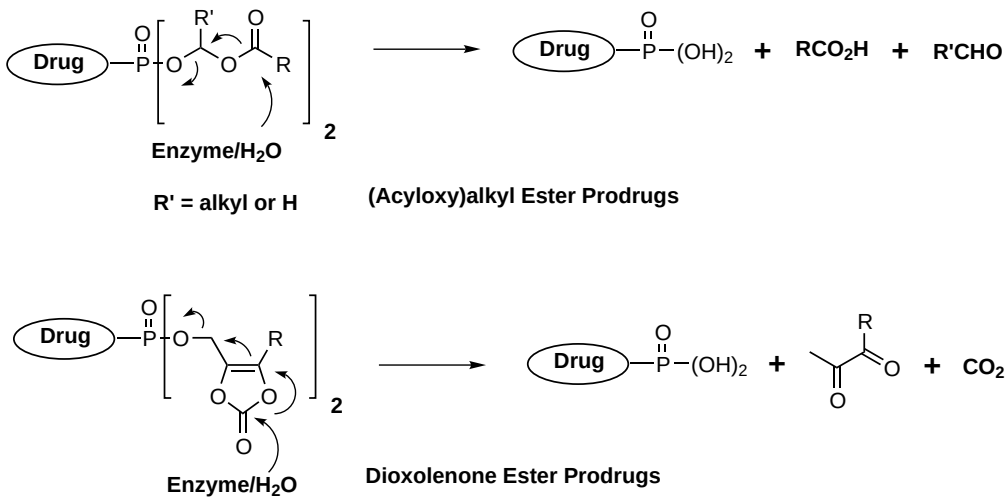


Figure 1.

Keywords: dioxolenone prodrug moieties; phosphonate prodrugs; squalene synthase inhibitors.

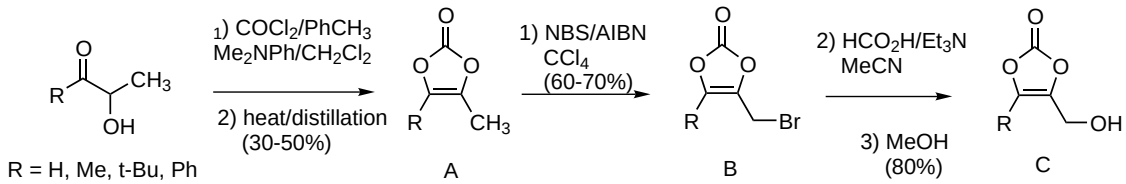
* Corresponding authors. Fax: 609-818-3460; e-mail: chongqing.sun@bms.com

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02386-3

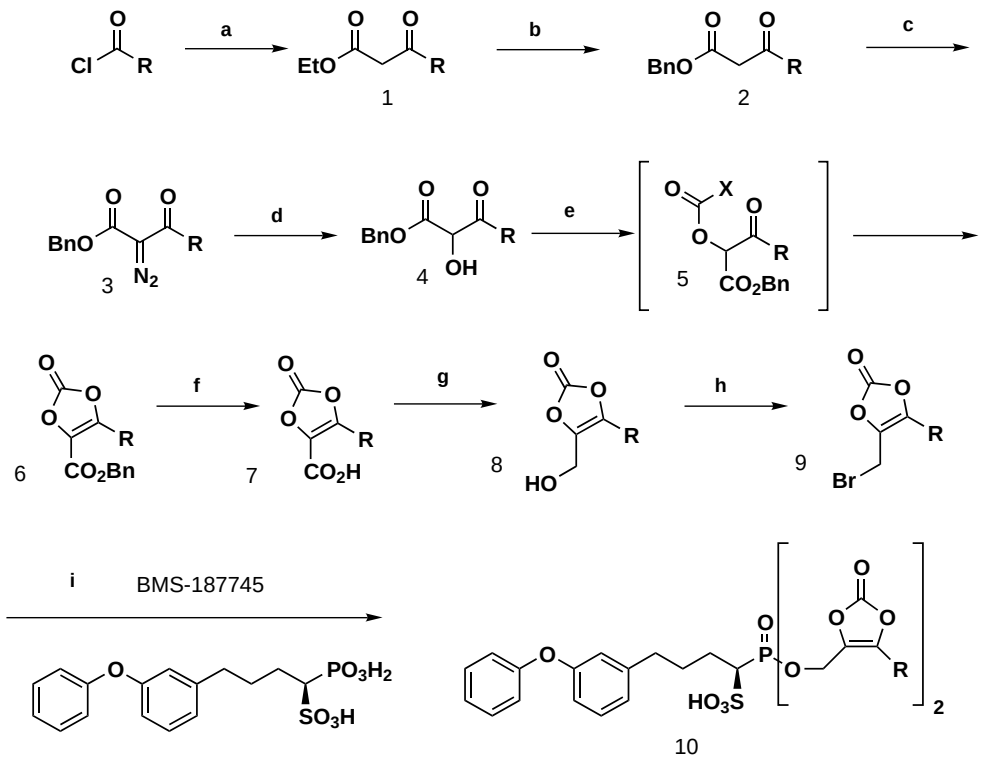
H), concerns regarding the potential toxicity associated with the formaldehyde by-product after bioconversion of the prodrug will always need to be addressed. Dioxolenone esters[4] comprise a different class of masked double-ester prodrug moiety which offer potential advantages over (acyloxy)alkyl esters because: (1) no asymmetric centers are present, and (2) enzymatic hydrolysis of dioxolenone esters releases relatively non-toxic carbon dioxide and α-dicarbonyl derivatives[5] rather than formaldehyde as by-products.

The variety of dioxolenones that could be used as prodrug moieties has to date been limited by available synthetic methods.[6] The literature synthetic sequence summarized in Scheme 1 relies upon allylic bromination of the dioxolenone intermediate **A** for the preparation of dioxolenone bromides **B**. Thus, this synthetic method is feasible with only a limited subset of substituents (i.e. R = H, CH_3, *t*-Bu or aryl). Dioxolenone alcohols **C** are obtained from bromides **B** by formate displacement followed by acid-catalyzed hydrolysis.[7]

As part of a program to identify suitable prodrugs of the novel squalene synthase inhibitor BMS-187745,[8] we wished to investigate modifications of the substituents (with diverse steric and electronic properties) at the 5-position of dioxolenone prodrug moieties as a means of modulating their susceptibility to enzymatic hydrolysis. Therefore, a general and efficient synthesis of 5-alkyl and 5-aryl substituted dioxolenones was required. The general synthetic sequence which we developed[9] is shown in Scheme 2. The requisite benzyl β-ketoesters **2** (R = alkyl or aryl) were readily available through acylation of ethyl malonate monoester with an acid chloride[10] and subsequent transesterification with benzyl alcohol.[11] Diazotization of β-ketoester **2** furnished the α-diazo β-keto ester **3**, which was then subjected to rhodium-mediated α,α-insertion of water to provide a key intermediate, the α-hydroxy β-keto ester **4**. Treatment of **4** with phosgene or a suitable synthetic equivalent (such as carbonyldiimidazole or triphosgene) in the presence of base furnished the corresponding dioxo-



Scheme 1.



Scheme 2. *Reaction conditions*: (a) $KO_2CCH_2CO_2Et$, $MgCl_2$, Et_3N/CH_3CN; (b) $PhCH_2OH$, DMAP (cat.), toluene/Δ; (c) 4-*N*-acetyl phenylsulfonylazide, Et_3N/CH_3CN; (d) $Rh_2(OAc)_4$ (cat.), THF/H_2O (2:1)/reflux; (e) $COCl_2$, iPr_2NEt; toluene OR carbonyldiimidazole, iPr_2NEt (cat.), CH_2Cl_2; (f) H_2, $Pd(OH)_2$, EtOH; (g) i. $(COCl)_2$, DMF (cat.), CH_2Cl_2, ii. Bu_4NBH_4, CH_2Cl_2; (h) Ph_3P, CBr_4, CH_2Cl_2; (i) iPr_2NEt, CH_3CN.

lenone ester **6** in good yield. The reaction presumably occurs via the initial *O*-acylation intermediate **5**, then undergoes enolization and subsequent cyclization to afford **6**. Hydrogenolysis of benzyl ester **6** provided the acid **7**, which was converted to the primary alcohol **8** via acid chloride formation followed by reduction (Table 1). Dioxolenone bromides **9** (obtained from bromination of alcohols **8**) were then successfully used to prepare the corresponding dioxolenone phosphonate prodrug esters **10** of BMS-187745 as shown in Scheme 2. The use of these carefully defined reaction conditions is necessary in order to avoid the racemization of the highly sensitive chiral center of BMS-187745. Di-esters **10** represent a unique phosphonate prodrug that has not been previously described.

In conclusion, the synthetic sequence described in this paper allows for the preparation of a wide variety of 5-substituted dioxolenone alcohols **8** and bromides **9** which are suitable as penultimate intermediates for the synthesis of carboxylic acid and phosphonic acid prodrugs. These novel substituted dioxolenone prodrugs should display a wide range of susceptibility to enzymatic hydrolysis as required. The utility of these substituted dioxolenones as prodrug moieties for acid-containing drugs, particularly phosphonic acids, will be reported in due course.

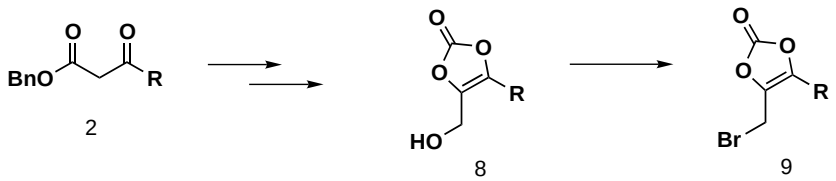
A representative set of experimental procedures for the preparation of dioxolenone alcohol **8c**, bromide **9c**, and the corresponding phosphonate prodrug **10c** is as follows:

Compound 3c: To a 0°C solution of β-keto ester **2c** (12.0 g, 51.3 mmol) and *p*-toluenesulfonylazide (12.3 g, 51.3 mmol) in CH_3CN (420 mL) was added Et_3N (21.4 mL, 15.4 mmol). The resulting yellow suspension was stirred at 0°C for 30 min, then at room temperature for 4 h. The mixture was concentrated in vacuo, and the solid residue was triturated with 2:1 ethyl ether and petroleum ether (2×150 mL). The filtrate was concentrated in vacuo to give an oily residue, which was chromatographed (SiO_2, 15:85 EtOAc/hexane) to provide compound **3c** as an oil (12.79 g, 96% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, 3H, $J=7.3$ Hz), 1.34 (m, 2H), 1.62 (m, 2H), 2.85 (m, 2H), 5.26 (s, 2H), 7.37 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 161.7, 135.6, 129.1, 129.1, 128.8, 67.3, 40.4, 26.8, 22.7, 14.2. Anal. calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.70; H, 6.10; N, 11.02.

Compound 4c: A solution of the diazo compound **3c** (12.7 g, 48.7 mmol) in THF (250 mL) and H_2O (120 mL) was refluxed with $Rh_2(OAc)_4$ (165 mg, 0.37 mmol) for 5 h and allowed to cool to room temperature. The mixture was concentrated in vacuo and the aqueous residue was extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to provide crude **4c** (12.04 g) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 3H, $J=7.3$ Hz), 1.21 (m, 2H), 1.52 (m, 2H), 2.53 (m, 2H), 4.81 (s, 1H), 5.24 (m, 2H), 7.36 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.1, 168.1, 134.6, 128.7, 128.6, 128.5, 77.7, 67.9, 38.3, 25.3, 21.9, 13.6. Anal. calcd for $C_{14}H_{18}O_4 \cdot 0.5H_2O$: C, 64.83; H, 7.39. Found: C, 64.84; H, 7.11.

Compound 6c: A 0°C solution of alcohol **4c** (11.76 g, 46.9 mmol) in dry THF (230 mL) was treated with carbonyldiimidazole (15.3 g, 94.4 mmol) followed by iPr$_2$NEt (336 μL, 1.9 mmol). After stirring at 0°C for 5 h and room temperature overnight, the mixture was concentrated in vacuo and the residue was partitioned between EtOAc and 5% aqueous $KHSO_4$. The separated organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an oily residue, which was chromatographed (SiO_2, 15:85 EtOAc/hexane) to provide pure **6c** (9.99 g, 77% yield from **3c**) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, $J=7.3$ Hz), 1.35 (m, 2H), 1.60 (m, 2H), 2.80 (t, 2H, $J=7.6$ Hz), 5.13 (s, 2H), 7.39 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 152.9, 150.1, 134.5, 129.4, 128.8, 128.8, 128.6, 67.5, 28.5, 24.6, 22.0, 13.5. Anal. calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.30; H, 6.07.

Table 1.



Entry	R	% yield of **8** from **2**	% yield of **9** from **8**
a	Et	53	63
b	*n*-Pr	31	87
c	*n*-Bu	52	79
d	*i*-Pr	44	86
e	*t*-Bu	54	84
f	4-CF_3-C_6H_4-	34	51
g	4-CH_3O-C_6H_4-	41	74

All new compounds gave satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR, MS).

Compound 7c: A solution of compound **6c** (9.98 g, 36.1 mmol) was stirred with $Pd(OH)_2$ on carbon (20%, 490 mg) in absolute EtOH (230 mL) under an atmosphere of hydrogen (balloon) for 70 min. Filtration and removal of volatiles in vacuo provided **7c** (6.56 g, 98%) as an off-white solid: mp 59–61°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 3H, $J=7.3$ Hz), 1.41 (m, 2H), 1.68 (m, 2H), 2.86 (t, 2H, $J=7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 155.5, 150.4, 129.3, 28.9, 25.3, 22.5, 14.0. Anal. calcd for $C_8H_{10}O_5$: C, 51.61; H, 5.41. Found: C, 51.61; H, 5.73.

Compound 8c: To a 0°C solution of acid **7c** (6.47 g, 34.7 mmol) and anhydrous DMF (350 μL) in dry CH_2Cl_2 (150 mL) was added dropwise oxalyl chloride (3.33 mL, 38.2 mmol). After addition was complete, the mixture was stirred at 0°C for 30 min, then at room temperature for 1 h before being concentrated and dried in vacuo. The residue was dissolved in dry CH_2Cl_2 (200 mL) and cooled to −78°C. To this solution was then added dropwise a solution of Bu_4NBH_4 (9.86 g, 38.3 mmol) in CH_2Cl_2 (60 mL) over 15 min (exothermic reaction). After stirring at −78°C for 1 h, the mixture was cautiously quenched with 0.1N aqueous HCl (100 mL) and allowed to warm up to room temperature. Volatiles were removed in vacuo and the residue was partitioned between EtOAc (200 mL) and H_2O (50 mL). The separated aqueous layer was saturated with NaCl and extracted with EtOAc (100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give an oily residue, which was chromatographed (SiO_2, 4:6 EtOAc/hexane) to provide pure **8c** as an oil (4.25 g) in 69% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, 3H, $J=7.5$ Hz), 1.37 (m, 2H), 1.59 (m, 2H), 2.38 (t, 1H, $J=6.2$ Hz), 2.45 (t, 2H, $J=7.5$ Hz), 4.41 (d, 2H, $J=6.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 141.3, 137.1, 53.4, 28.8, 23.5, 22.0, 13.7. Anal. calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 56.11; H, 7.34.

Compound 9c: To a 0°C solution of alcohol **8c** (2.00 g, 11.6 mmol) in CH_2Cl_2 (150 mL) were successively added CBr_4 (4.62 g, 13.9 mmol) and Ph_3P (3.35 g, 12.8 mmol). After stirring for 30 min at 0°C and 1 h at room temperature, volatiles were removed in vacuo and the residue was chromatographed (SiO_2, 2:8 EtOAc/hexane) to provide **9c** (2.15 g, 79%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, 3H, $J=7.5$ Hz), 1.39 (m, 2H), 1.60 (m, 2H), 2.45 (t, 2H, $J=7.5$ Hz), 4.19 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 141.6, 134.4, 28.3, 23.6, 21.9, 17.8, 13.6. Anal. calcd for $C_8H_{11}BrO_3$: C, 40.88; H, 4.72; Br, 33.99. Found: C, 40.90; H, 4.71; Br, 33.93.

Compound 10c: A solution of the triacid BMS-187745 (830 mg, 2.15 mmol) and iPr$_2$NEt (1.27 mL, 7.34 mmol) in anhydrous CH_3CN (10 mL) was treated with bromide **9c** (1.73 g, 7.33 mmol) in anhydrous CH_3CN (8 mL). After stirring at room temperature for 5 days, the mixture was diluted with EtOAc (100 mL) and successively washed with 5% KH_2PO_4 buffer (pH 2, 3×40 mL), 5% KH_2PO_4 buffer (pH 6, 40 mL) and saturated aqueous KCl (40 mL), dried over Na_2SO_4, filtered and concentrated in vacuo to give an oily residue. This crude product was purified using preparative HPLC (2-EM Merck, RP Select B column (5×50 cm) eluting with 57% isocratic solvent B: solvent A (B = 95% CH_3CN/5% H_2O; A = 95% H_2O/5% CH_3CN; A is buffered with 0.04 M NH_4OAc/acetic acid to pH 5.5). The desired fractions were combined and lyophilized to give **10c** (ammonium salt) as a clear gum (925 mg, 61% yield); MS: $[M+H]^+=695$; ^{1}H NMR (400 MHz, CD_3OD): δ 0.92 (m, 6H), 1.36 (m, 4H), 1.54 (m, 4H), 1.93–2.21 (m, 4H), 2.52 (m, 4H), 2.61 (m, 2H), 3.32–3.45 (m, 1H), 4.92 (d, 2H, $J=8.6$ Hz), 4.98 (d, 2H, $J=8.6$ Hz), 6.75 (m, 1H), 6.84 (s, 1H), 6.95 (d, 3H, $J=8.5$ Hz), 7.06 (m, 1H), 7.20 (m, 1H), 7.32 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 158.9, 158.7, 153.8, 145.5, 145.2, 135.5, 135.4, 130.8, 130.7, 124.6, 124.2, 120.1, 119.8, 117.3, 60.8, 59.4, 58.0, 57.2, 36.5, 30.9, 29.7, 28.7, 24.1, 23.0, 14.0. Anal. calcd for $C_{32}H_{42}NO_{13}PS\cdot0.11H_2O$: C, 53.86; H, 5.96; N, 1.96; P, 4.34; S, 4.49. Found: C, 53.78; H, 6.03; N, 2.04; P, 4.40; S, 4.40.

References

1. (a) Bundgaard, H. In *A Textbook of Drug Design and Development*; Krogsgaard-Larsen, P.; Bundgaard, H., Eds.; Langhorne: Harwood Academic, 1991; pp. 113–191; (b) Krise, J. P.; Stella, V. J. *Adv. Drug Deliv. Rev.* **1996**, *19*, 287–310; (c) Freeman, S.; Ross, K. C. In *Progress in Medicinal Chemistry*; Ellis, G. P.; Luscombe, D. K., Eds.; Elsevier Science BV: Amsterdam, 1997; Vol. 34, pp. 111–147.
2. Bundgaard, H. *Adv. Drug Deliv. Rev.* **1989**, *3*, 39–65.
3. Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; DeForrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G.; Schwartz, J.; Natarajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1988**, *31*, 1148–1160.
4. (a) Saari, W. S.; Halczenko, W.; Cochran, D. W.; Dobrinska, M. R.; Vincek, W. C.; Titus, D. C.; Gaul, S. L.; Sweet, C. S. *J. Med Chem.* **1984**, *27*, 713–717; (b) Sakamoto, F.; Ikeda, S.; Hirayama, R.; Moriyama, M.; Sotomura, M.; Tsukamoto, G. *Chem. Pharm. Bull.* **1987**, *35*, 642–646; (c) Miyauchi, M.; Suzuki, K.; Endo, R.; Kawamto, I. *Chem. Pharm. Bull.* **1990**, *38*, 1077–1078; (d) Ryono, D. E.; Lloyd, J.; Poss, M. A.; Bird, J. E.; Buote, J.; Chong, S.; Dejneka, T.; Dickson, K. E.; Gu, Z.; Mathers, P.; Moreland, S.; Morrison, R. A.; Petrillo, E. W.; Powell, J. R.; Schaeffer, T.; Spitzmiller, E. R.; White, R. E. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 201–206.
5. Alexander, J.; Bindra, D. S.; Glass, J. D.; Holahan, M. A.; Renyer, M. L.; Rork, G. S.; Sitko, G. R.; Stranieri, M. T.; Stupienski, R. F.; Veerapanane, H.; Cook, J. J. *J. Med. Chem.* **1996**, *39*, 480–486 and references cited therein.
6. Sakamoto, F.; Ikeda, S.; Tsukamoto, G. *Chem. Pharm. Bull.* **1984**, *32*, 2241–2248 and references cited therein.
7. Alpegiani, M.; Zarini, F.; Perrone, E. *Synth. Commun.* **1992**, *22*, 1277–1282.
8. Lawrence, M. R.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J. V. H.; Magnin, D. R.; Sulsky, R. B.; DiMarco, J. D.; Gougoutas, J. Z.; Beyer, B. D.; Taylor, S. C.; Lan, S.-J.; Ciosek, C. P., Jr.; Harrity, T. W.; Jolibois, K. G.; Kunselman, L. K.; Slusarchyk, D. A. *J. Am. Chem. Soc.* **1996**, *118*, 11668–11669 and references cited therein.
9. Cheng, P. T. W.; Sun, Chong-Qing.; Poss, M. A. *US Patent* 5,610,314, 1997.
10. Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. *Synthesis* **1993**, 290–292.
11. Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618–3619.