Chemoselective Etherification of Benzyl Alcohols Using 2,4,6-Trichloro-1,3,5-triazine and Methanol or Ethanol Catalyzed by Dimethyl Sulfoxide

Lili Sun, Yuping Guo, Guisheng Peng, Chunbao Li*

Department of Chemistry, College of Science, Tianjin University, 300072 Tianjin, P. R. of China
Fax +86(22)27403475; E-mail: lichunbao@tju.edu.cn

Received 4 June 2008; revised 22 July 2008

Abstract: An efficient method for the transformation of benzyl alcohols into their methyl or ethyl ethers has been established using 2,4,6-trichloro-1,3,5-triazine (TCT) and dimethyl sulfoxide in methanol or ethanol. This procedure chemoselectively converts benzylic hydroxys into their methyl or ethyl ethers in the presence of aliphatic or phenolic hydroxys.

Key words: benzyl alcohols, chemoselectivity, ethers, sulfoxide, 2,4,6-trichloro-1,3,5-triazine

Ethers are of great importance as intermediates and products in organic synthesis, and the conversion of alcohols into ethers is one of the most important synthetic procedures.[1] Frequently used methods for the transformation of alcohols to ethers are the reactions of alcohols or their salts with different alkylating reagents, such as alkyl halides,[2] diazomethane,[3] and methyl trifluoromethanesulfonate.[4] The dehydration of alcohols using protonic acids[5] (H_3PO_4 and H_2SO_4), Lewis acids[6] [$ZnCl_2$, $Mg(ClO_4)_2$, $FeCl_3$, and $Fe(ClO_4)_3$], iodine,[7] and dimethyl sulfoxide at high temperature[8] has also been reported. However, each method has certain limitations with regard to scope and reaction conditions.[5a,9]

In our research into the chlorination of benzyl alcohols, it was found that 4-methoxybenzyl alcohol could be converted into its methyl ether in excellent yield by treatment of the alcohol with 2,4,6-trichloro-1,3,5-triazine (TCT) and dimethyl sulfoxide in dry methanol. Therefore, it became of interest to study this ether-forming reaction with other benzyl alcohols.

Table 1 summarizes some mixed ethers synthesized by this procedure. Although dimethyl sulfoxide was shown to be a catalyst by the conversion of 4-methoxybenzyl alcohol (Table 1, entry 1) into its methyl ether using 0.1 equiv of dimethyl sulfoxide, the best results were obtained when it was used in an approximately equimolar amount. A decreased amount of TCT caused longer reaction times and lower yields. Portionwise addition of dimethyl sulfoxide in methanol to the mixture of benzyl alcohol and TCT in methanol gave better results than addition as one portion. Thus, the procedure was based on portionwise addition of dimethyl sulfoxide (1 equiv) in dry methanol or ethanol (5 mL) to a solution of benzyl alcohol (1 equiv) and TCT (1.2 equiv) in dry methanol or ethanol (5 mL).

It is apparent from Table 1 that ether formation coincides quite favorably with what would be expected from the structures of the benzyl alcohols in terms of the ease of carbocation formation. Most of the alcohols in Table 1 were converted into their methyl or ethyl ethers in moderate to high yields under our conditions. For cinnamyl alcohol (Table 1, entry 8), the formation of the carbocation is not as easy as the other benzyl alcohols bearing electron-donating groups, which results in a prolonged reaction time (18 h) and a small amount of chloride byproduct. A definite trend towards decreased yields and prolonged times was observed from the formation of methyl and ethyl ethers (Table 1, entries 1 and 4 vs entries 10 and 11). This effect could well be a manifestation of the progressive decrease in the dielectric constant (32.63 and 24.3 for MeOH and EtOH, respectively)[10] and consistent with the carbocation mechanism (Scheme 2). When the elimination reaction competed with etherification, the yield of the desired ether could be increased by performing the reaction at lower temperature (Table 1, entry 9). Under our reaction conditions, the desired ethers could be prepared starting from acid-labile substrates (Table 1, entries 2 and 6) although in moderate yield for Table 1, entry 6.

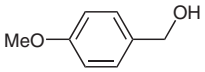
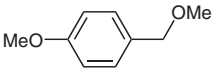
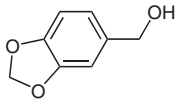
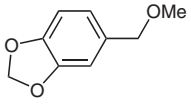
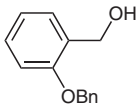
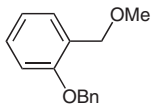
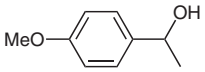
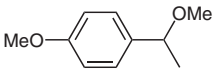
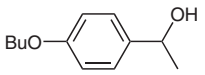
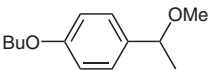
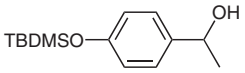
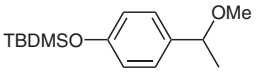
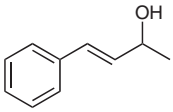
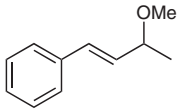
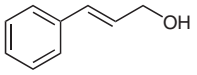
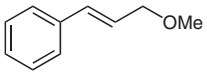
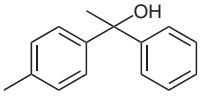
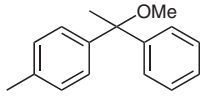
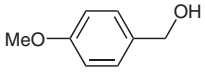
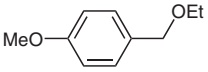
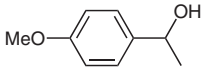
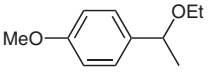
Most interestingly, the method is clearly inefficient for aliphatic alcohols, in which the carbocation can not be formed as easily as in benzyl alcohols. This provides a chemoselective etherification of benzylic hydroxys in the presence of aliphatic or phenolic hydroxys (Table 2 and Scheme 1). For the substrates in Table 2 and Scheme 1, all the benzylic hydroxys were converted into methyl or ethyl ethers while the aliphatic or phenolic hydroxys were left intact.

Using the above procedure, we converted 2-(hydroxymethyl)estradiol into 2-(methoxymethyl)estradiol (Scheme 1), which was previously synthesized from estradiol through a five-step procedure with protection and deprotection steps in the research of its effect as an inhibitor of tubulin polymerization and for cytotoxicity.[11] The five-step synthetic route to 2-(methoxymethyl)estradiol was shortened to a three-step route using our procedure without protection and deprotection steps (Scheme 1).[12,13] This makes it much easier to prepare the target compound for biological tests.

In order to verify our assumption that the reaction proceeds with the formation of a carbocation intermediate,

SYNTHESIS 2008, No. 21, pp 3487–3491
Advanced online publication: 16.10.2008
DOI: 10.1055/s-0028-1083184; Art ID: F12508SS

Table 1 Preparation of Methyl or Ethyl Ethers from Benzyl Alcohols Using TCT and Dimethyl Sulfoxide[a]

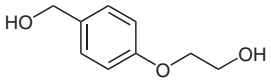
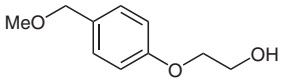
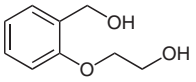
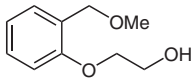
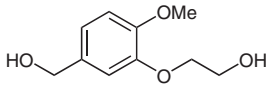
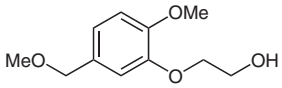
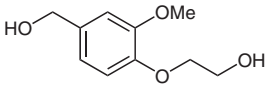
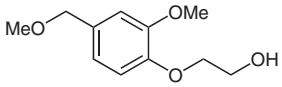
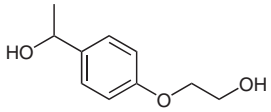
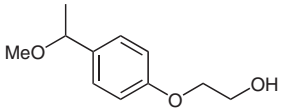
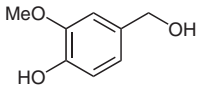
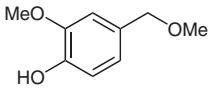
Entry	Substrate	Product	Time[b]	Yield (%)
1			3 h (9 h[c])	91 (79[c])
2			5 h (12 h[c])	94 (75[c])
3[d]			5 h	62
4			15 min	77
5			25 min	91
6			30 min	40
7			1.5 h	69
8[e]			18 h	55
9[f]			4 h	80 (7[g])
10			7.5 h	75
11			20 min	69

[a] To a mixture of alcohol (1 equiv) and TCT (1.2 equiv) in anhyd MeOH or EtOH was added DMSO (1 equiv) in anhyd MeOH or EtOH portionwise.
[b] Time for complete disappearance of alcohols. The reactions were worked up 4 hours later for an easier separation of products.
[c] Catalyzed by 0.1 equiv of DMSO.
[d] The reaction was performed at the reflux temperature of MeOH.
[e] Plus 5% of cinnamyl chloride and 27% recovered cinnamyl alcohol.
[f] The reaction was performed at 0 °C.
[g] Yield of elimination product.

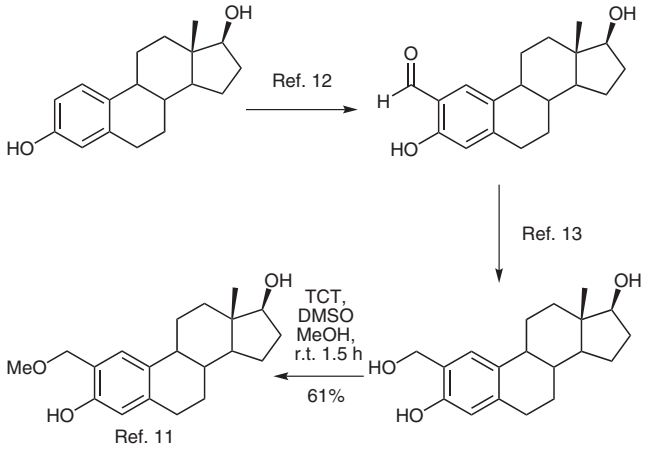
we treated an optically active alcohol, (*S*,*E*)-4-phenylbut-3-en-2-ol, $[\alpha]_D^{20}$ –32.1 (*c* 0.018, $CHCl_3$) with TCT and dimethyl sulfoxide in methanol. It was observed that racemization occurred under our reaction conditions. This is also in agreement with the results reported by Salehi et al.[6c] On the basis of the above experiments, a plausible mechanism is proposed (Scheme 2). The adduct **I** of TCT and dimethyl sulfoxide reacts with the benzyl alcohol to form a dimethyl alkoxysulfonium salt **II**, which decomposes to form carbocation **III** and regenerate dimethyl sulfoxide. Nucleophilic attack of methanol or ethanol on **III** produces the methyl or ethyl ether, respectively. This reaction also demonstrates that the substitution capability of neutral nucleophiles such as methanol and ethanol in higher concentration can exceed that of negatively charged nucleophiles such as chloride in lower concentration.

In conclusion, a new method for the transformation of benzyl alcohols into their methyl or ethyl ethers has been developed using 2,4,6-trichloro-1,3,5-triazine (TCT) and dimethyl sulfoxide. The procedure reported herein is operationally simple, and requires inexpensive and commercial available reagents. This procedure has been proven to be chemoselective for benzylic hydroxys in the presence of aliphatic or phenolic hydroxys, which constitutes a useful tool for medicinal and organic chemistry.

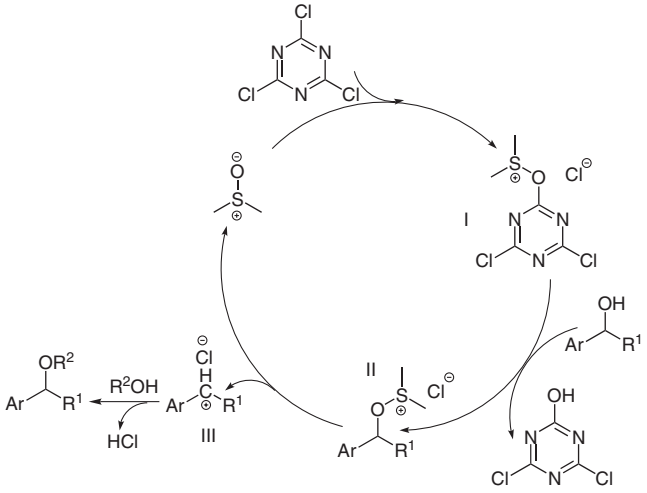
Table 2 Chemoselective Etherification of Benzylic Hydroxys in the Presence of Aliphatic or Phenolic Hydroxys[a]

Entry	Substrate	Product	Time[b]	Yield (%)
1			6.5 h	65
2[c]			5.5 h	62
3			5 h	71
4			5 h	76
5			35 min	84
6			45 min	84

[a] To a mixture of alcohol (1 equiv) and TCT (1.2 equiv) in anhyd MeOH was added DMSO (1 equiv) in anhyd MeOH portionwise.
[b] Time for complete disappearance of alcohols. The reactions were worked up 4 hours later for a easier separation of products
[c] The reaction was performed at the reflux temperature of MeOH.



Scheme 1



Scheme 2

All of the chemicals were obtained from commercial sources or prepared according to standard methods. All the chemicals and solvents used in reactions were dried by standard procedures prior to use. IR spectra were recorded on a Bio-Rad Exalibur FTS3000 spectrophotometer. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded on a Varian Oxford 500 spectrometer relative to TMS (^{1}H) or $CDCl_3$ (^{13}C). MS (EI) were obtained on a Thermo Finnigan TRACE-DSQ spectrometer. Elemental analyses for C, H and N were performed on a Yanaco CHNCORNER MF-3 elemental analyzer, and the analytical results were within ±0.4% of the theoretical values. All novel compounds were fully characterized, all known compounds (Table 1, entries 1–5, 7–11;[14–20] Table 2, entry 6[21]) were characterized and the data compared to the literature.

1-Methoxy-4-(methoxymethyl)benzene (Table 1, Entry 1); Typical Procedure

To a soln of 4-methoxybenzyl alcohol (189 mg, 1.37 mmol) and TCT (101 mg, 1.64 mmol) in anhyd MeOH (5 mL) was added DMSO (107 mg, 1.37 mmol) in anhyd MeOH (5 mL) portionwise. The mixture was stirred at r.t. for 3 h (completion, TLC monitoring). The mixture was added to EtOAc (50 mL) and the organic phase was washed with H_2O (30 mL), sat. $NaHCO_3$ (30 mL), and brine (30 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo to give the crude product which was then purified by chromatography (silica gel, petroleum ether–Et_2O, 8:1) to afford 1-methoxy-4-(methoxymethyl)benzene (190 mg, 91%).

tert-Butyl[4-(1-methoxyethyl)phenoxy]dimethylsilane (Table 1, Entry 6)
Yield: 99 mg (40%); colorless oil.

IR (KBr): 3425, 2957, 2830, 2859, 1609, 1510, 1256, 1117, 1103, 916, 839, 780 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.5 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 4.23 (q, *J* = 6.4 Hz, 1 H), 3.19 (s, 3 H), 1.41 (d, *J* = 6.4 Hz, 3 H), 0.98 (s, 9 H), 0.20 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 136.0, 127.3, 119.8, 79.1, 55.2, 25.6, 23.6, 18.1, –4.4.

MS: *m*/*z* (%) = 266 (10, M^+), 251 (60), 234 (26), 209 (32), 196 (9), 177 (100), 151 (20).

Anal. Calcd for $C_{15}H_{26}O_2Si$: C, 67.61; H, 9.84. Found: C, 67.57; H, 9.86.

2-[4-(Methoxymethyl)phenoxy]ethanol (Table 2, Entry 1)
Yield: 140 mg (65%); colorless oil.

IR (KBr): 3398, 2924, 2860, 2818, 1611, 1512, 1458, 1364, 1245, 1174, 1083, 1057, 918, 822 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.6 Hz, 2 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 4.39 (s, 2 H), 4.08 (t, *J* = 4.5 Hz, 2 H), 3.95 (t, *J* = 4.5 Hz, 2 H), 3.36 (s, 3 H), 2.81 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2, 130.6, 129.3, 114.4, 74.2, 69.2, 61.3, 57.7.

MS: *m*/*z* (%) = 182 (82, M^+), 167 (5), 151 (50), 137 (49), 121 (24), 107 (100), 89 (18).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.96; H, 7.77.

2-[2-(Methoxymethyl)phenoxy]ethanol (Table 2, Entry 2)
Yield: 165 mg (62%); colorless oil.

IR (KBr): 3428, 2927, 2877, 1601, 1490, 1450, 1240, 1080, 1050, 915, 750 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.30 (m, 2 H), 6.97 (t, *J* = 7.3 Hz, 1 H), 6.92 (d, *J* = 8.2 Hz, 1 H), 4.52 (s, 2 H), 4.18 (t, *J* = 4.5 Hz, 2 H), 3.88 (t, *J* = 4.5 Hz, 2 H), 3.38 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.1, 130.2, 129.4, 126.6, 120.9, 113.1, 70.7, 70.5, 61.1, 57.8.

MS: *m*/*z* (%) = 182 (78, M^+), 167 (35), 137 (100), 133 (35), 121 (60), 107 (60), 106 (72), 91 (45), 78 (56), 77 (28), 45 (30).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.93; H, 7.71.

2-[2-Methoxy-5-(methoxymethyl)phenoxy]ethanol (Table 2, Entry 3)
Yield: 153 mg (71%); colorless oil.

IR (KBr): 3423, 2935, 1586, 1517, 1427, 1262, 1236, 1164, 1139, 1086, 1027, 905, 810, 765 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 1.8 Hz, 1 H), 6.90 (dd, *J* = 1.8 Hz, *J* = 8.1 Hz, 1 H), 6.84 (d, *J* = 8.1 Hz, 1 H), 4.37 (s, 2 H), 4.13 (t, *J* = 4.5 Hz, 2 H), 3.93 (t, *J* = 4.5 Hz, 2 H), 3.85 (s, 3 H), 3.36 (s, 3 H), 2.65 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.0, 147.9, 130.8, 121.1, 113.8, 111.2, 74.3, 70.9, 61.0, 57.8, 55.8.

MS: *m*/*z* (%) = 212 (70, M^+), 181 (44), 167 (26), 137 (100).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.08; H, 7.57.

2-[2-Methoxy-4-(methoxymethyl)phenoxy]ethanol (Table 2, Entry 4)
Yield: 163 mg (76%); colorless oil.

IR (KBr): 3448, 2935, 2867, 1593, 1515, 1458, 1420, 1364, 1262, 1235, 1140, 1087, 1033, 905, 810 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.90 (m, 1 H), 6.87 (s, 1 H), 6.84 (dd, *J* = 1.4 Hz, *J* = 8.1 Hz, 1 H), 4.39 (s, 2 H), 4.11 (t, *J* = 4.5 Hz, 2 H), 3.92 (t, *J* = 4.5 Hz, 2 H), 3.87 (s, 3 H), 3.37 (s, 3 H), 2.77 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.6, 147.5, 131.7, 120.3, 114.0, 111.2, 74.4, 71.1, 61.0, 57.8, 55.7.

MS: *m*/*z* (%) = 212 (47, M^+), 181 (11), 167 (25), 137 (100).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.11; H, 7.59.

2-[4-(1-Methoxyethyl)phenoxy]ethanol (Table 2, Entry 5)
Yield: 180 mg (84%); colorless oil.

IR (KBr): 3419, 2925, 2873, 1608, 1583, 1512, 1461, 1366, 1246, 1096, 1076, 1052, 922, 834 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.6 Hz, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 4.25 (q, *J* = 6.4 Hz, 1 H), 4.09 (t, *J* = 4.5 Hz, 2 H), 3.96 (t, *J* = 4.5 Hz, 2 H), 3.20 (s, 3 H), 1.42 (d, *J* = 6.4 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.0, 135.8, 127.3, 114.3, 79.0, 69.1, 61.2, 56.1, 55.2.

MS: *m*/*z* (%) = 196 (15, M^+), 181 (100), 164 (20), 137 (70), 120 (52), 91 (20).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.44; H, 8.25.

Acknowledgment

We thank NSFC (20572078) for financial support.

References

(1) Larock, R. C. In *Comprehensive Organic Transformations*, 2nd ed., Vol. 2; John Wiley & Sons: Indianapolis, **1999**, 889.
(2) (a) Hutchins, R. O.; Taffer, I. M. *J. Org. Chem.* **1983**, *48*, 1360. (b) *The Chemistry of the Ether Linkage*; Patai, S., Ed.; Interscience: New York, **1967**, 445.
(3) (a) Ohno, K.; Nishiyama, H.; Nagase, H. *Tetrahedron Lett.* **1979**, *20*, 4405. (b) Caserio, M. C.; Roberts, J. D.; Neeman, M.; Johnson, W. S. *J. Am. Chem. Soc.* **1958**, *80*, 2584.
(4) (a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042. (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171.
(5) (a) Curtin, D. Y.; Leskowitz, S. *J. Am. Chem. Soc.* **1951**, *73*, 2630. (b) Norris, J. F.; Rigby, G. W. *J. Am. Chem. Soc.* **1932**, *54*, 2088. (c) Smith, H. A.; Smith, R. J. *J. Am. Chem. Soc.* **1948**, *70*, 2400.
(6) (a) Kim, S.; Chung, K. N.; Yang, S. *J. Org. Chem.* **1987**, *52*, 3917. (b) De Mico, A.; Margarita, R.; Piancatelli, G. *Tetrahedron Lett.* **1995**, *36*, 2679. (c) Salehi, P.; Iranpoor, N.; Behbahani, F. K. *Tetrahedron* **1998**, *54*, 943.
(7) Jenner, G. *Tetrahedron Lett.* **1988**, *29*, 2445.
(8) Emert, J.; Goldenberg, M.; Chiu, G. L.; Valeri, A. *J. Org. Chem.* **1977**, *42*, 2012.
(9) Traynellis, V. J.; Hergenrother, W. L.; Hanson, H. T.; Valicenti, J. A. *J. Org. Chem.* **1964**, *29*, 123.
(10) Lange, N. A. In *Handbook of Chemistry*, 9th ed.; Handbook Pubs. Inc.: Sandusky, **1956**, 1222.

(11) Edsall, A. B.; Mohanakrishnan, A. K.; Yang, D.; Fanwick, P. E.; Hamel, E.; Hanson, A. D.; Agoston, G. E.; Cushman, M. *J. Med. Chem.* **2004**, *47*, 5126.
(12) Peters, R. H.; Chao, W.-R.; Sato, B.; Shigeno, K.; Zaveri, N. T.; Tanabe, M. *Steroids* **2003**, *68*, 97.
(13) Lovely, C. J.; Gilbert, N. E.; Liberto, M. M.; Sharp, D. W.; Lin, Y. C.; Brueggemeier, R. W. *J. Med. Chem.* **1996**, *39*, 1917.
(14) Kumar, H. M. S.; Anjaneyulu, S.; Joyasawal, S.; Chakravarthy, P. P.; Kumar, V. N.; Yadav, J. S. *J. Indian Chem. Soc.* **2007**, *84*, 189.
(15) Kirmse, W.; Konrad, W.; Oezkir, I. S. *Tetrahedron* **1997**, *53*, 9935.
(16) Srikrishna, A.; Viswajanani, R. *J. Indian Chem. Soc.* **2000**, *77*, 621.
(17) Dem'yanovich, V. M.; Khlebnikov, V. A. *Russ. J. Org. Chem.* **1994**, *30*, 255.
(18) Malkov, A. V.; Baxendale, I. R.; Dvořak, D.; Mansfield, D. J.; Kočovský, P. *J. Org. Chem.* **1999**, *64*, 2737.
(19) Selivanov, B. A.; Bil'kis, I. I.; Shteingarts, V. D. *J. Org. Chem. USSR (Engl. Trans.)* **1992**, *28*, 1357.
(20) Hurd, C. D.; Iwashige, T. *J. Org. Chem.* **1959**, *24*, 1321.
(21) Cook, S. P.; Danishefsky, S. J. *Org. Lett.* **2006**, *8*, 5693.