Effect of the Acidic Component on the Mitsunobu Inversion of a Sterically Hindered Alcohol

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Since its introduction in 1967, the Mitsunobu reaction has been widely utilized in the refunctionalization of alcohols and, in particular, inversion of this moiety.[1] In general, this method proves efficacious for a variety of substrates providing useful yields of inverted product under mild, essentially neutral reaction conditions (PPh_3, $EtO_2CN{=}NCO_2Et$, RCO_2H). Given the immense popularity of the Mitsunobu protocol,[2] we became intrigued by several reports in the literature documenting dramatic increases in product yield when the acidic component (RCO_2H) of the reaction is simply changed from benzoic acid to 4-nitrobenzoic acid. Early references to this phenomenon include primary and secondary substrates such as nucleosides[3] and propargylic alcohols,[4] respectively. Moreover, 4-nitrobenzoic acid has also been shown to be a particularly effective coupling partner for sterically encumbered alcohols,[5] a finding which has led to practical modifications of the Mitsunobu reaction.[6,7] Despite these observations, the origin(s) of this interesting phenomenon has recieved little attention.[6a] To address this issue, we have systematically investigated the critical role of the carboxylic acid in the Mitsunobu inversion process for sterically hindered alcohols.

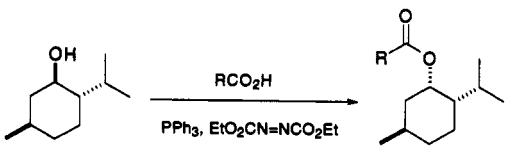
Menthol (1) was selected as an ideal substrate for studying the effects of the acid in the Mistunobu reaction. The isopropyl functionality provides the prerequisite steric hindrance about the adjacent alcohol moiety while the carbocyclic nature allows for simple detemination of stereochemical inversion via ^{1}H-NMR coupling constants and/or chemical shifts. Initially, the appropriateness of this model was demonstrated by reacting 1 under Mitsunobu protocol using 4-nitrobenzoic and benzoic acid in separate experiments under identical reaction conditions. As expected, significantly higher yields of inverted ester 2 were obtained when the former aryl acid was employed (77% *vs* 20% for benzoic acid). Since the primary discriminating factor between these two acids is their respective dissociation constants ($4\text{-}O_2NC_6H_4CO_2H$, pK_a = 3.41; $PhCO_2H$, pK_a = 4.16), we were interested in determining whether a correlation exists between the acidity of the carboxylic species and the efficacy of the reaction (gaged by yield).[8]

We initally focused on functionalized acetic acids with pK_a's ranging from approximately 1 to 5. When the parent acid (CH_3CO_2H, pK_a = 4.75) is reacted with menthol, PPh_3, and diethyl azodicarboxylate, the starting alcohol is recovered intact and no inverted product is recovered from the reaction mixture (Table I). However, employing more acidic species such as chloroacetic acid[9] (pK_a = 2.85) under the same reaction conditions gives the desired product in 60% yield. Extending the scope to even stronger proton donating sources such as dichloroacetic acid (pK_a = 1.29) results in exclusive acid-induced esterification of the secondary alcohol rather than the desired inversion regardless of the order of addition.[10] While predominant retention of stereochemical integrity is somewhat unex-

Table I. Variation of the Carboxylic Acid Component in the Mitsunobu Inversion of Menthol (1 → 2)[a]

carboxylic acid	solvent	pK_a[11]	yield (%)
Cl_2CHCO_2H	PhH	1.29	*b*
$ClCH_2CO_2H$	PhH	2.86	60
CH_3CO_2H	PhH	4.76	0
$2\text{-}O_2NC_6H_4CO_2H$	PhH	2.16	33
$4\text{-}O_2NC_6H_4CO_2H$	PhH	3.41	77
$4\text{-}O_2NC_6H_4CO_2H$	THF	3.41	83
$4\text{-}O_2NC_6H_4CO_2H$	CH_3CN	3.41	6
$4\text{-}O_2NC_6H_4CO_2H$	CH_2Cl_2	3.41	3
$3\text{-}O_2NC_6H_4CO_2H$	PhH	3.47	55
$4\text{-}CNC_6H_4CO_2H$	PhH	3.55	60
$4\text{-}MeSO_2C_6H_4CO_2H$	PhH	3.64	61
$2\text{-}CH_3C_6H_4CO_2H$	PhH	3.91	<5
$4\text{-}ClC_6H_4CO_2H$	PhH	3.98	54
$4\text{-}BrC_6H_4CO_2H$	PhH	4.00	51
$2\text{-}CH_3OC_6H_4CO_2H$	PhH	4.09	0
$4\text{-}FC_6H_4CO_2H$	PhH	4.14	23
$C_6H_5CO_2H$	PhH	4.19	20
$4\text{-}CH_3C_6H_4CO_2H$	PhH	4.36	26
$4\text{-}CH_3OC_6H_4CO_2H$	PhH	4.47	19

[a] All reactions were run with identical stoichiometries of alcohol, triphenylphosphine, and diethyl azodicarboxylate. [b] Esterification with retention of stereochemistry is observed.



1 2

RCO_2H	yield (%)
$R = 4\text{-}NO_2C_6H_4$	77
R = Ph	20

(1) For reviews see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Castro, B. R. *Org. React.* **1983**, *29*, 1. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(2) The Mitsunobu reaction has evolved into one of the primary synthetic tools for inverting alcohol stereochemistry as evidenced by over 1100 citations to Mitsunobu's 1981 review on the subject.

(3) Mitsunobu, O.; Kimura, J. ; Fujisawa, Y. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 245.

(4) Jarosz, S.; Glodek, J.; Zamojski, A. *Carbohydr. Res.* **1987**, *163*, 289.

(5) (a) Brandstetter, H. H.; Zbiral, E. *Helv. Chim. Acta.* **1978**, *61*, 1832. (b) Eaton P. E.; Jobe, P. G.; Reingold, I. D. *J. Am. Chem. Soc.* **1984**, *106*, 6437. (c) Kocienski, P. J.; Street, S. D. A.; Yeates, C.; Cambell, S. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2171. (d) Use of 3,5-dinitrobenzoic acid has also proven effective; see: Brussani, G.; Ley, S. V.; Wright, J. L.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 303.

(6) (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) For applications of this modification see: Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1549. Klar, U.; Pletsch, A.; Skubulla, W.; Vorbuggen, H. *Biomed. Chem. Lett.* **1992**, 445. Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Hartmann, M. *J. Org. Chem.* **1992**, *57*, 1070. Valerde, S.; Lopez, J. C.; Gomez, A. M.; Garcia-Ochoa, S. *J. Org. Chem.* **1992**, *57*, 1613. Maruoka, K.; Sato, J.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3749. Bessodes, M.; Saiah, M.; Antonakis, K. *J. Org. Chem.* **1992**, *57*, 4441. Caine, D.; Kotian, P. L. *J. Org. Chem.* **1992**, *57*, 6587. Coleman, R. S.; Fraser, J. R. *J. Org. Chem.* **1993**, *58*, 385. Wovkulich, P. M.; Shankaran, K.; Kiegiel, J.; Uskokovic, M. R. *J. Org. Chem.* **1993**, *58*, 832. Carey, J. S.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 3935. Giodot, J. P.; Gall, T. L. *Tetrahedron Lett.* **1993**, *34*, 4647. Keck, G. E.; Park, M.; Krishnamurthy, D. *J. Org. Chem.* **1993**, *58*, 3787.

(7) Mori and co-workers advocate the use of 3,5-dinitrobenzoic in the Mitsunobu reaction to enhance crystallization of the inverted product (no improvements in yields are reported). For representative examples see: Mori, K.; Ikunaka, I. *Tetrahdron* **1984**, *40*, 3471. Mori, K.; Otsuka, T.; Oda, M. *Tetrahdron* **1984**, *40*, 2929.

(8) Previous studies of the Mitsunobu reacton with imidodicarbonates (RO_2CNHCO_2R) indicate a dependence on NH acidity.

(9) The use of chloroacetic acid has been reported to be effective for the inversion of sterically congested alcohols: Saiah, M.; Bessodes, M.; Antonakis, K. *Tetrahedron Lett.* **1992**, *33*, 4317.

0022-3263/94/1959-0234$04.50/0

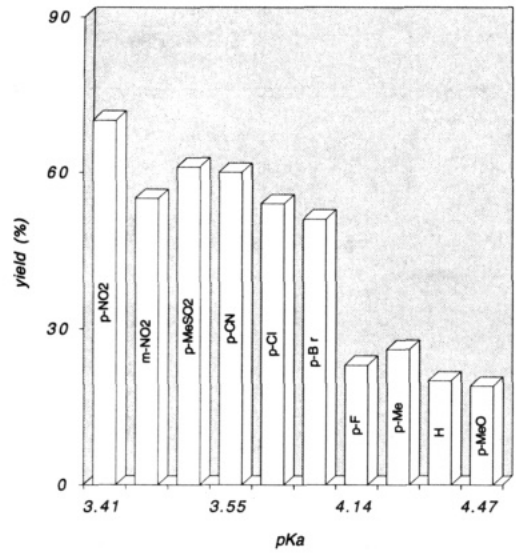


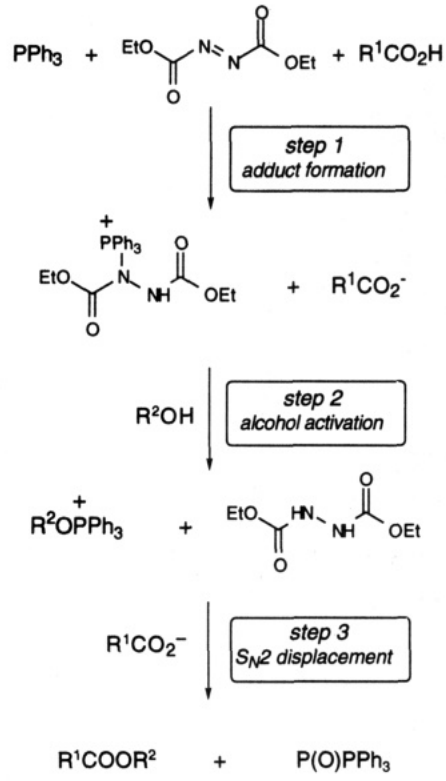
Figure 1. Plot of pK_a vs yield for substituted acids in the Mitsunobu inversion of menthol.

pected, it is not entirely clear whether to ascribe this lack of inversion to the increase in acidity or the accompanying increase in steric bulk of the carboxylate nucleophile as a result of the additional chloro substituent. Thus, while there appears to be a relationship between acidity and efficacy in the limited number of acetic acid derivatives examined (compare CH_3CO_2H to $ClCH_2CO_2H$), we elected to explore *para*- and *meta*-substituted benzoic acids which would allow for a more comprehensive study without possible misinterpretation due to inherent steric factors of the nucleophile.

Substituent effects in the Mitsunobu reaction for various aryl carboxylic acids are summarized in Table I along with their corresponding acid dissociation constants and reaction yields. Examination of the data reveals a distinct trend in which use of stronger aryl acids, such as 4-nitro-, 4-cyano-, and 4-(methylsulfonyl)benzoic acids, results in good yields of inverted product (60–83%). In contrast, weaker acids such as benzoic, 4-toluic, and 4-anisic give appreciably diminished yields (19–26%) when compared to their more acidic counterparts. A graphical illustration of these results is shown in Figure 1. *It is interesting to note that benzoic acid, historically one of the most popular for Mitsunobu inversions, is one of the least attractive coupling partners.* The *ortho*-substituted cases also follow the observed pK_a trend although the yields are consistently lower, presumably due to steric considerations. The solvent employed also appears to play a dramatic role in reaction efficacy, with some solvents (THF, benzene) proving notably superior to others (CH_3CN, CH_2Cl_2).[12]

The general features of the Mitsunobu reaction have been well-documented (Scheme I).[13] In particular, carboxylate basicity has been shown to play an integral role in defining whether alcohol activation (step 2) or S_N2 displacement (step 3) is rate determining. Hughes and co-workers[13f] have shown that less acidic (more basic) carboxylate species dictate a slow S_N2 reaction. However, with more acidic (less basic) species, the rates of alcohol activation and S_N2 displacement (steps 2 and 3, respectively) become comparable. We observed that the dependence of reaction efficacy on pK_a (Figure 1) appears consistent with this mechanistic interpretation, *i.e.*, rate enhancement of the slow step, and further demonstrates the importance of the acid in partitioning the reactive intermediates in the Mitsunobu process.[14]

Scheme I



In summary, Mitsunobu inversion of menthol is dramatically influenced by the acidic component. There appears to be a relationship between the dissociation constant of the acid and the overall efficacy of the reaction with more acidic species generally providing higher yields of inverted product. It is also apparent that a variety of electon-withdrawing substituents on the aryl acid (*p*- or *m*-NO_2, *p*-SO_2Me, and *p*-CN) provide synthetically useful yields thereby adding further overall utility to this important method.

(10) Use of cyanoacetic acid (pK_a = 2.43) gives a 2:1 mixture of inversion/retention in 62% combined yield.

(11) Acid dissociation constants were obtained from: Jencks, W. P.; Regensein, J. In *Handbook of Biochemistry and Molecular Biology*; Sober, H. A., Ed.; Chemical Rubber Company.: Cleveland, OH, 1968; p J 150 (acetic acids). Kortum, G.; Vogel, W.; Andrussow, K. *Pure Appl. Chem.* **1960**, *1*, 190 (aryl acids).

(12) The reasons for such a marked dependence on the reaction medium are not entirely clear although solvent effects for Mistunobu inversions have been documented. For example, see: Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1977**, *60* 417.

(13) For leading references on the mechanism of the Mitsunobu reaction see: (a) Guthrie, R. D.; Jenkins, I. D. *Aust. J. Chem.* **1982**, *35*, 767. (b) Grochowski, E.; Hilton, B. D.; Kupper, R. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 6876. (c) von Itzstein, M.; Jenkins, I. D. *Aust. J. Chem.* **1983**, *36*, 557. (d) Adam, W.; Narita, N.; Nishizawa, Y. *J. Am. Chem. Soc.* **1984**, *106*, 1843. (e) Varasi, M.; Walker, K. A. M.; Maddox, M. L. *J. Org. Chem.* **1987**, *52*, 4235. (f) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487. (g) Crich, D.; Dyker, H.; Harris, R. J. *J. Org. Chem.* **1989**, *54*, 257. (h) Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045, 3049.

(14) Jenkins *et al.* (ref 13h) have also shown the Mistunobu process to be highly dependent on the acid with more acidic species favoring a reaction equilibria in which the requisite oxyphosphonium intermediate is formed at the expense of a pentacoordinate dialkylphosphorane. While this interpretation is also consistent with our findings, the presence of this pentacoordinate intermediate appears contingent on the concentration of the acidic component. All examples in this study were performed in a manner consistent with the Hughes' experimental protocol, *i.e.*, betaine formation in the presence of the acid. Moreover, identical stoichiometries of acid/alcohol were used throughout.

Experimental Section

Anhydrous tetrahydrofuran, dichloromethane, and acetonitrile were purchased from Aldrich Chemical Co. Benzene was distilled from CaH_2 immediately prior to use. Menthol, triphenylphosphine, and diethyl azodicarboxylate were purchased from commercial sources and employed without further purification. ^{1}H-NMR and ^{13}C-NMR were measured at 300 and 75 MHz, respectively, with a Nicolet QE-300. Flash chromatography[15] was performed using silica gel purchased from EM Science (230–400 mesh). Radial chromatography was performed on a Chromatotron (Harrison Research, Palo Alto, CA) using 1-, 2-, or 4-mm silica gel coated plates. All reactions were conducted in oven-dried glassware under a nitrogen atmosphere.

Representative Experimental Procedure: (1*S*,2*S*,5*R*)-1-(4-Nitrobenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol.[16] A 250-mL, three-necked, round-bottomed flask was equipped with a stir bar, a nitrogen inlet, a septum, and a thermometer. The flask was charged with (1*R*,2*S*,5*R*)-(−)-menthol (3.00 g, 19.2 mmol), 4-nitrobenzoic acid (12.9 g, 77.2 mmol), triphenylphosphine (20.1 g, 76.6 mmol), and tetrahydrofuran (150 mL). The flask was immersed in an ice bath, and diethyl azodicarboxylate (12.1 mL, 77 mmol) was added in a dropwise fashion at a rate such that the reaction temperature was maintained below 10 °C. Upon completion of the addition, the flask was removed from the ice bath and the solution allowed to stir at room temperature overnight. Excess solvent and other volatile reaction components were completely removed under reduced pressure on a rotary evaporator and then under high vacuum (approximately 0.1 mmHg for 1 h). The resulting thick syrup was dissolved in 20 mL of ether and the solution allowed to stand at room temperature overnight whereupon a white precipitate formed. The mixture was then sonicated while 10 mL of hexanes was slowly added. The white solid was then vacuum filtered and the filter cake washed with 100 mL of 50% ether–hexanes. Removal of solvent from the filtrate under reduced pressure gave a yellow oil which was dissolved in 10 mL of methylene chloride and then diluted with 40 mL of 8% ether–hexanes. The solution was applied to a flash chromatography column and eluted with 8% ether–hexanes to give 4.72 g (83%) of pure nitrobenzoate ester as a white crystalline solid: mp = 93–95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 8.9 Hz, 2H), 8.34 (d, J = 8.5 Hz, 2H), 5.60 (s, 1H), 2.20 (m, 1H), 1.90–2.10 (complex, 2H), 1.68–1.88 (m, 1H), 1.50–1.67 (complex, 2H), 0.87–1.31 (complex, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) 163.8, 150.3, 136.3, 130.5, 123.4, 73.0, 46.8, 29.0, 34.6, 29.3, 26.7, 25.3, 22.0, 20.8, 20.0; IR ($CDCl_3$) 1726, 1540, 1293 cm^{-1}; LRMS (CI) 306 (MH, 100), 139; $C_{17}H_{23}NO_4$, C (66.87, found 66.8), H (7.59, found 7.43), N (4.59, found 4.77); HRMS (CI) calcd for $C_{17}H_{24}NO_4$ (306.1705), found 306.1696.

(1*S*,2*S*,5*R*)-1-(Chloroacetoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.27 (s, 1H), 4.03 (s, 2H), 1.90–2.01 (m, 1H), 1.28–1.80 (series of m, 7H), 0.80–0.90 (complex 10H); IR (cell, $CDCl_3$) 1728 cm^{-1}; $C_{12}H_{21}O_2Cl$, C (61.93, found 62.04), H (9.09, found 8.82), Cl (15.23, found 15.49).

(1*S*,2*S*,5*R*)-1-(3-Nitrobenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.96 (s, 1H), 8.55 (m, 2H), 7.79 (t, J = 3 Hz, 1H), 5.64 (s, 1H), 2.20–2.30 (m, 1H), 1.00–2.09 (series of m, 17H); IR (cell, $CDCl_3$) 1718 cm^{-1}; FAB$^+$ 306.5.

(1*S*,2*S*,5*R*)-1-(2-Nitrobenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR (DMSO-d_6, 300 MHz) 8.01 (m, 1H), 7.82 (m, 3H), 5.38 (s, 1H), 2.50 (m 1H), 2.0 (dt, 1H), 1.66 (br d ,4H), 1.0–1.62 (series of m, 5H) 0.81–0.92 (complex, 10H); FAB$^+$ 306.6.

(1*S*,2*S*,5*R*)-1-(4-(Methylsulfonyl)benzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.24 (d, J = 8 Hz, 2H), 8.05 (d, J = 8 Hz, 2H), 5.52 (s, 1H), 3.07 (s, 3H), 2.10 (m, 1H), 0.9–1.94 (complex, 17H); IR (cell, $CDCl_3$) 1716 cm^{-1}; $C_{18}H_{26}O_4S$ C (63.88, found 64.12), H (7.74, found 7.52), S (9.47, found 9.49).

(1*S*,2*S*,5*R*)-1-(4-Cyanobenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H), 5.18 (s, 1H), 1.04–1.79 (series of m, 8H), 0.50–0.99 (complex, 10H); IR (cell, $CDCl_3$) 1716 cm^{-1}; FAB$^+$ 286.3.

(1*S*,2*S*,5*R*)-1-(4-Chlorobenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.41 (d, J = 8 Hz, 2H), 8.34 (d, J = 8 Hz, 2H), 5.60 (s, 1H), 2.21 (m, 1H), 0.99–2.0 (complex, 17H); IR (cell, $CDCl_3$) 1711 cm^{-1}; FAB$^+$ 295.2.

(1*S*,2*S*,5*R*)-1-(4-Bromobenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, J = 8 Hz, 2H), 7.49 (d, J = 8 Hz, 2H), 5.38 (s, 1H), 2.00 (m, 1H), 1.35–1.80 (series of m, 7H), 0.70–1.015 (complex, 10H); IR (cell, $CDCl_3$) 1710 cm^{-1}; FAB$^+$ 339.2.

(1*S*,2*S*,5*R*)-1-(4-Fluorobenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.04 (m, 2H), 7.10 (m, 2H) 5.41 (s, 1H), 2.02–2.18 (m, 1H), 0.80–1.91 (series of m, 17H); IR (cell, $CDCl_3$) 1709 cm^{-1}; FAB$^+$ 279.3.

(1*S*,2*S*,5*R*)-1-(4-Methylbenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.01 (d, J = 8 Hz, 2H), 7.35 (d, J = 8 Hz, 2H), 5.50 (s, 1H), 2.50 (s, 3H), 2.11–2.19 (m, 1H), 1.09–2.00 (series of m, 8H), 0.80–1.05 (complex, 10H); IR (cell, $CDCl_3$) 1705 cm^{-1}; FAB$^+$ 275.3.

(1*S*,2*S*,5*R*)-1-Benzoyl-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 7.98 (d, J = 8 Hz, 2H), 7.64 (t, J = 8 Hz, 1H), 7.52 (t, 8 Hz), 5.39 (s, 1H), 1.94 (m, 1H), 1.051.84 (series of m, 7H), 0.80–1.04 (complex, 10H); IR (cell, $CDCl_3$) 1709 cm^{-1}; FAB$^+$ 261.2.

(1*S*,2*S*,5*R*)-1-(4-Methoxybenzoyl)-2-(1-methylethyl)-5-methylcyclohexan-1-ol: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, J = 7 Hz, 2H), 6.86 (d, J = 7 Hz, 2H), 5.38 (s, 1H), 3.80 (s, 3H), 0.98–2.10 (series of m, 8H), 0.79–0.98 (complex, 10H); IR (cell, $CDCl_3$) 1701 cm^{-1}; FAB$^+$ 291.3.

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Supplementary Material Available: ^{1}H-NMR spectra for the following inverted esters of menthol (R): $ClCH_2CO_2R$, 2-$O_2NC_6H_4CO_2R$, 4-$O_2NC_6H_4CO_2R$, 3-$O_2NC_6H_4CO_2R$, 4-$CNC_6H_4CO_2R$, 4-$MeSO_2C_6H_4CO_2H$, 4-$ClC_6H_4CO_2H$, 4-$BrC_6H_4CO_2R$, 2-$CH_3OC_6H_4CO_2R$, 4-$FC_6H_4CO_2R$, $C_6H_5CO_2R$, 4-$CH_3C_6H_4CO_2R$, and 4-$CH_3OC_6H_4CO_2R$ (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(16) Dodge, J. A.; Nissen, J. S.; Presnell, M. *Org. Synth.*, submitted.