# Stereochemistry of the Monoalkylation of (1*R*)-3-*endo*-(*p*-Methoxybenzyl)isobornyl Propionate

Byung Ick Seo, David E. Lewis\*1

Department of Chemistry, South Dakota State University, Box 2202, Brookings, SD 57007-0896 USA Fax +1(715)8364979; E-mail: lewisd@uwec.edu *Received 7 September 2001; revised 30 April 2002* 

**Abstract:** The alkylation of the lithium enolate of (1R)-3-endo-(*p*-methoxybenzyl)isobornyl propionate in THF gives predominantly the (*R*)-2-methylalkanoic esters in de's of 25–42%. The structure of the alkyl halide does not affect the outcome, although the most reactive halides give the greatest de levels. The formation of the enolate in THF–HMPA reverses the stereochemistry of the alkylation with ethyl bromide from 42% *R* to 23% *S*. The stereochemistry of the reaction is interpreted in terms of a conformational shift on deprotonation of the ester.

**Key words:** benzylisobornyl esters, alkylations, stereoselectivity, lithium enolates, steric hindrance

The alkylation of simple ester enolates as a method for the formation of chiral  $\alpha$ -alkyl carboxylic acids and the corresponding aldehydes and primary alcohols has met with widely varying success, giving alkylated products with de's from less than 50% to over 95% depending on the chiral auxiliary used.<sup>2</sup> In previous papers,<sup>3,4</sup> we have reported the synthesis of 3-endo-(p-methoxybenzyl)isoborneol (1) and the conformations of its esters based on their <sup>1</sup>H NMR spectra and the single crystal Xray structure analysis of 3-endo-(p-methoxybenzyl)isobornyl p-nitrobenzoate (2). The structure obtained is presented in Figure 1. This structure shows that the aromatic ring in these esters is ideally located to completely shield one face of the carbonyl group and the  $\alpha$ -carbon. Bearing in mind that solid-state conformations are not always predictive of solution-phase conformations, in light of the <sup>1</sup>H NMR evidence, this still strongly suggested that the 3-endo-benzylisoborneols might function as useful chiral auxiliaries for alkylation reactions.



**Figure 1** The structure of 3-*endo*-(*p*-methoxybenzyl)isobornyl *p*-nitrobenzoate (2).

Synthesis 2002, No. 10, Print: 30 07 2002. Art Id.1437-210X,E;2002,0,10,1391,1397,ftx,en;M04301SS.pdf. © Georg Thieme Verlag Stuttgart · New York ISSN 0039-7881 Herein, we describe the results of a systematic study of the monoalkylation of the lithium enolates of the propionate ester 3 with a variety of alkyl halides.

The starting propionate ester **3** could be prepared by acylation of the alcohol **1** with propionic anhydride in pyridine or by acylation of its sodium alkoxide with propionyl chloride. The lithium enolate **4e** [(*E*)-**4**] or **4z** [(*Z*)-**4**] was straightforwardly prepared by deprotonation of the ester with lithium diisopropylamide (LDA) in THF at  $-78 \text{ }^{\circ}\text{C}$ (Figure 2). Trapping experiments with D<sub>2</sub>O indicated that the deprotonation is restricted to the  $\alpha$ -protons of the acyl group, and that it is complete within two minutes at  $-78 \text{ }^{\circ}\text{C}$ , despite the relatively hindered nature of the ester.



Figure 2 The structures of the propionate ester 3 and the enolates 4e, 4z.

The lithium enolate was alkylated with a variety of alkyl halides, each reaction being carried out by addition of excess alkyl halide to the cold (-78 °C) solution of the enolate.<sup>5</sup> The reaction with ethyl bromide is illustrated in the Scheme.



Scheme

From this reaction, five products were isolated: the alcohol **1**, the monoalkylated esters, **5a** and **6a**, the dialkylated ester, **7a**, and the  $\beta$ -keto ester **8**. Under the reaction conditions, the two diastereoisomeric  $\alpha$ -methylcarboxylate esters **5a** and **6a**, were obtained as an inseparable mixture in the disappointingly low ratio of less than 3:1. The results are summarized in the Table. Of the dialkylated esters, we explicitly isolated only **7a** and **7b**; lesser yields of the corresponding esters **7c**–**g** may be formed with larger alkyl halides, but these esters were not present in quantities sufficient to isolate. The isolation of the  $\beta$ -keto ester **8** was undertaken only in the reaction with ethyl bromide.

Table Alkylation of 1 by Alkyl Halides in THF

RX	5	6	Yield (%)	de (%) <sup>a</sup>	7
EtBr	5a	6a	60	42 ( <i>R</i> )	<b>7a</b> (11) <sup>b</sup>
EtBr (HMPA-THF)	5a	6a	60	24 ( $S$ )	-
<i>n</i> -BuBr	5b	6b	65	42(R)	<b>7b</b> (4) <sup>b</sup>
<i>i</i> -PrI	5c	6c	25	40(R)	-
c-C <sub>5</sub> H <sub>11</sub> Br	5d	6d	26	34(R)	-
i-BuI	5e	6e	23	26 ( $R$ )	-
CH <sub>2</sub> =CHCH <sub>2</sub> Br	5f	6f	46	40(R)	-
CH <sub>2</sub> =C(Me)CH <sub>2</sub> Cl	5g	6g	46	42 ( <i>R</i> )	-

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy using peak heights at 200 MHz.

<sup>b</sup> Isolated percent yields of chromatographically homogeneous compounds.

The relative abundance of the two diastereoisomeric  $\alpha$ methylcarboxylate esters 5a and 6a obtained by deprotonation of 3 in THF and alkylation with ethyl bromide was reversed when the deprotonation and alkylation were carried out in 23% HMPA in THF. This result is in accord with the predictions of the Ireland model<sup>6</sup> for deprotonation of esters: although the effects of solvent on enolate geometry may be more subtle than previously assumed,<sup>7</sup> the Ireland model predicts that deprotonation in THF-HMPA will give predominantly the (Z)-O-enolate 4z and deprotonation in THF alone will give predominantly the (E)-O-enolate 4e. While the effects of enolate aggregation cannot be eliminated as the primary cause of this stereochemical reversal, the observed stereochemistry is consistent with the alkylation being under kinetic control, with the ratio of the  $\alpha$ -methylcarboxylates obtained being determined by the stereochemistry of the ester enolate. The observed sterochemistry also suggests that the rate of stereochemical inversion of the ester enolate is slow when compared with the rate of the alkylation reaction and that any subsequent equilibration of the product is slow enough not to affect the stereochemistry of the final product mixture in any substantive way. Given the extended reaction time for alkylation, inversion of enolate geometry cannot be eliminated as a possible origin of the poor stereoselectivity of the alkylation. However, unless aggregation effects are almost entirely responsible for the reversal of alkylation stereochemistry on incorporation of HMPA into the solvent, the Curtin–Hammett Principle makes it difficult to reconcile that stereochemical reversal with stereochemical inversion of the enolate occurring more rapidly than its alkylation or other reactions. Unfortunately, all our attempts to isolate an enol silyl ether from this reaction – which would answer this stereochemical question unambiguously – have failed. Although one may speculate that this may be due, in part, to the sterically congested location of the enolate oxygen atom, we have no direct evidence to bear on this question.

Since the diastereoisomeric  $\alpha$ -methylcarboxylate esters co-elute under all conditions studied to date, the determination of de's and the assignment of absolute configuration of the new chiral center by HPLC was not possible in this system. However, in the 200 MHz <sup>1</sup>H NMR spectrum of the propionate ester **3** the diastereotopic protons of the acyl methylene group resonate at very similar, but discernibly different chemical shifts ( $\delta = 2.189$  and 2.190). This suggested that it might be possible to assign the absolute configuration to the  $\alpha$ -methylcarboxylate esters by <sup>1</sup>H NMR spectroscopy. The preliminary examination of the <sup>1</sup>H NMR spectra of the mixed  $\alpha$ -methylcarboxylate esters reinforced this hypothesis.

In order to assign the absolute configuration of the esters produced, a compound of known absolute configuration was needed to provide the baseline chemical shift data for one of the two diastereoisomers. This ester of known configuration was obtained by derivatization of the sodium salt of the alcohol 1 with (S,S)-(+)-2-methylbutanoic anhydride. This gave a single stereoisomeric ester 6a; derivatization of the racemic acid via its acid chloride or the mixed phosphoric anhydride afforded an inseparable mixture of the two esters 5a and 6a, under the same conditions (see experimental part). The <sup>1</sup>H NMR spectra of the ester 6a and of the mixture of the two esters showed that the chemical shifts of three protons were sensitive to the absolute configuration of the acyl group: the benzyl protons and the doublet resonance of the  $\alpha$ -methyl group of the acyl moiety. When the spectrum of the ester 6a was compared with the spectra of the esters prepared by alkylation of 3 with ethyl bromide, it was clear that this ester of known absolute configuration corresponds to the minor isomer formed in the alkylation reaction. Thus, the major isomer formed by alkylation of (1R)-3 in THF is the ester of (R)-2-methylbutanoic acid, while when the alkylation of the same ester is carried out in HMPA-THF, the major isomer is the (S)-2-methylbutanoate ester. The chemical shift patterns in the <sup>1</sup>H NMR spectra of the mixed  $\alpha$ -methylcarboxylates formed in the alkylation reactions indicated that this is general: alkylation of (1R)-3 gives the (R)-2-methylcarboxylate ester as the major product. The <sup>1</sup>H NMR spectra of all the mixtures of monoalkylated products showed the same pattern of chemical shifts for the benzyl protons of the auxiliary and the  $\alpha$ -methyl group of the acyl group, thus allowing the stereochemistry of all

alkylated products to be assigned by analogy with the ethyl compound.

The observed lack of stereoselectivity may be due to two possible causes: a conformational change in the enolate on deprotonation of the ester, resulting in loss of shielding by the aryl ring, or the interconversion of the (E)-O- and (Z)-O-enolates. While enolate inversion may account for the observed stereochemistry of the alkylation, we suggest that the reversal of stereochemistry when HMPA is added to the solvent renders this rationalization less attractive than the alternative, based on a conformational change on deprotonation of the ester. However, such simple stereochemical isomerization of the enolate cannot be eliminated from consideration by our results.

Thus, we suggest that the observed stereochemistry of the alkylation reactions – which is exactly the opposite of that which would be predicted on the basis of the conformation of the starting ester – is better rationalized on the basis of a major conformational change on deprotonation of the ester. We suggest that the conformation changes from A below (reminiscent of the starting ester) to B; this moves the aromatic ring to a position anti to the carbinol carbon (C-2 of the bornane ring system) of the ester, and away from the  $\alpha$ -carbon of the enolate (Figure 3). Given that the electron-poor carbonyl group of the ester becomes electron-rich in the enolate anion, and that conformation **B** increases the distance between the two electron-rich groups while approximating another energy minimum of the starting ester, we suggest that this may not be an unreasonable rationalization of the observed results. AM1 calculations using the trimethylsilyl enol ether as a model suggest that the enolate anion may, in fact, adopt several conformations of similar energy. AM1 Calculations indicate that conformations A and B, separated by a barrier of approximately 4.5 kcal/mole, are the lowest-energy conformations available to the system; conformation  $\mathbf{B}$  is lower in energy by 0.57 kcal/mol.



Figure 3 Sterochemical definition of the alkylation products based on conformations  ${\bf A}$  and  ${\bf B}$ .

In conformation **B**, the aromatic ring is not located in a position where it will affect the approach the alkyl halide to the enolate, with a result that the C-10 methyl group of the bornane ring system becomes the dominant stereocontrolling feature of the molecule. Under these circumstances, the stereochemical bias of the alkylation reaction is reversed and reduced, with a result that the (R)- $\alpha$ -methylcarboxylate ester becomes the major isomer of a 2:1 mixture of diastereoisomers obtained by alkylation of the (1R)propionate ester.

In the alkylation of (1R)-3, we observed that secondary halides and branched halides all gave de's below 30% compared to unbranched, reactive halides which all gave de's above 40%. In addition, the chemical yields of alkylated products from reactions with secondary alkyl halides were generally lower than the chemical yields from reactions with primary halides. This result is counter-intuitive: in general, one expects that as the alkyl halide becomes more sterically demanding, the effects of the steric blocking groups around the prochiral center should become more pronounced and the de levels should increase – one expects significantly higher de's when the alkylating agent is branched.

We suggest that the origin of this stereochemical result is in three potential competing reactions available to the initially-formed lithium enolate. The enolate may undergo alkylation to give the esters **5** and **6**, it may undergo stereochemical inversion to interconvert **4e** and **4z**, or it may undergo Claisen condensation to give the  $\beta$ -keto ester **8** and the alcohol **1**. The observed results are consistent with competing Claisen condensation and stereochemical inversion of the enolate being slower than the alkylation with small, reactive halides, but comparable in rate to alkylation with more bulky halides. An alternative rationalization, pointed out by a reviewer, may be more likely: it is possible that  $\beta$ -elimination from the branched alkyl halides competes more successfully with the alkylation reaction.

In summary, (1R)-3-endo-(p-methoxybenzyl)isobornyl propionate (3) reacts rapidly with LDA in THF to give the lithium enolate. This enolate reacts with alkyl halides to give an inseparable mixture of the esters of the 2-methylalkanoic acid 5 and 6 as the major products in disappointingly low de's of 25-42% R. The stereochemistry of the reaction is reversed when the lithium enolate is generated in HMPA-THF. The structure of the alkyl halide does not markedly affect the outcome, although the most reactive halides give the greatest de levels, a result which is interpreted in terms of competing stereochemical inversion and Claisen condensation reactions available to the lithium ester enolate. The stereochemical outcome of the monoalkylation is consistent with a conformational shift on deprotonation of the ester that moves the  $\alpha$ -carbon of the enolate into a position where the C-10 methyl group becomes the major stereochemical determining factor.

Melting points were determined using an electrically heated hotstage microscope, and are uncorrected. NMR spectra were recorded in CDCl<sub>3</sub> solution using a Varian Gemini-200 NMR Spectrometer at 200 MHz for <sup>1</sup>H and 50 MHz for <sup>13</sup>C. Chemical shifts are reported as d (ppm) downfield from internal Me<sub>4</sub>Si (0) for <sup>1</sup>H and the center peak of CDCl<sub>3</sub> (77.1) for <sup>13</sup>C. Assignments of peaks labeled \* may be interchanged. Chemical shift assignments are based on the numbering system given in Figure 4.



Figure 4 Numbering system for benzylisobornyl esters.

IR spectra were recorded as neat films or by diffuse reflectance from KBr on a Bio-Rad FTS-60A Fourier transform IR spectrophotomer; peak positions are calibrated against polystyrene (1601 cm<sup>-1</sup>). EI mass spectra were recorded using a Kratos MS25 RFA mass spectrometer at 70 eV. GC-MS spectrometry was carried out using a Finnigan 1020B automated GC-MS spectrometer at 70 eV. High resolution EI mass spectra were determined on chromatographically homogenous (HPLC on silica gel) samples which were held under vacuum (<1 mm Hg) for 24 h prior to measurement. Optical rotations were taken using a Cenco polarimeter and a 10 cm cell at the sodium D line (589 nm); the solvent and concentration (g mL<sup>-1</sup>) are reported; all values reported are the average of at least 5 determinations from each side. Column chromatography was carried out using 70-230 mesh silica gel (Aldrich) and the indicated eluting solvent. TLC was carried out on Merck silica gel 60F<sub>254</sub>. HPLC was carried out using a Waters Associates system with an Alltech silica gel column (1  $\mu$  silica gel packing, 25 cm  $\times$  10 mm ID), differential detection, and isocratic hexane-EtOAc eluents and flow rates indicated.

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out under dry argon in flame-dried glassware. (1*R*)-3-endo-(p-Methoxybenzyl)isoborneol was prepared by the published procedure.<sup>4</sup> THF was distilled from sodium benzophenone ketyl immediately prior to use. Other solvents were fractionally distilled prior to use. BuLi was obtained from Aldrich as a 10.0 M solution in hexane and was used as obtained. Lithium diisopropylamide (LDA) was obtained from Aldrich as a 1.5 M solution in cyclohexane and was used as obtained. Pyridine was refluxed over KOH, distilled, and stored over KOH. Hexamethylphosphoramide (HMPA) was refluxed over CaH<sub>2</sub> for 1 h, distilled under vacuum, and stored over CaH<sub>2</sub>. All other reagents were used as obtained from Aldrich.

#### (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Propanoate (3)

The alcohol **1** (0.85 g, 3 mmol) was dissolved in anhyd pyridine (30 mL), and propionic anhydride (1.5 g, 11.5 mmol) was added. The solution was stirred at r.t. until TLC analysis indicated that esterification was complete (72 h). H<sub>2</sub>O (10 mL) was added to the solution, and the reaction mixture was stirred for 1 h. The mixture was then diluted with Et<sub>2</sub>O (50 mL), and extracted with 10% aq HCl (3 × 30 mL). The combined aqueous layers were saturated with NaCl and extracted with Et<sub>2</sub>O (2 × 25 mL). The combined Et<sub>2</sub>O layers were washed with sat. aq NaHCO<sub>3</sub> (2 × 25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The ester **3** was thus obtained as a colorless oil (0.97 g, 94%);  $[a]_D^{25}$ –19.5 (*c* = 10.8, CHCl<sub>3</sub>).

<sup>1</sup>H NMR: δ = 7.07 (d, 2 H, J = 8.7 Hz, ArH), 6.79 (d, 2 H, J = 8.7 Hz, ArH), 4.48 (d, 1 H, J = 4.2 Hz, C2-H), 3.75 (s, 3 H, OCH<sub>3</sub>), 2.83 (dd, 1 H, J = 7.3, 13.6 Hz, C1′-H<sub>*R*</sub>), 2.57 (dd, 1 H, J = 8.8, 13.6 Hz, C1′-H<sub>*S*</sub>), 2.37 (complex, 1 H, C3-H), 2.190 (q, 1 H, J = 7.6 Hz, C2″′-H), 2.189 (q, 1 H, J = 7.6 Hz, C2″′-H), 1.10–1.70 (complex, 5 H, C4-H, C5-H, C6-H), 1.04 (t, 3 H, J = 7.6 Hz, C3″′-H), 0.99 (s, 3 H, C10-H), 0.82 (s, 3 H, C9-H), 0.75 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 173.7 (C=O), 157.7 (C4"), 133.1 (C1"), 129.5 (C2"), 113.6 (C3"), 85.4 (C2), 55.1 (OCH<sub>3</sub>), 49.8 (C1), 48.9 (C4), 47.9 (C3), 47.7 (C7), 35.7 (C6), 34.0 (C5), 27.9 (C2""), 20.4 (C9), 19.4 (C8), 11.4 (C10), 9.3 (C3"").

EIMS: *m*/*z* (rel. abundance) = 330 (M<sup>+</sup>, 14), 256(40), 161 (16), 160 (100), 122 (11), 121 (67).

HRMS-EI: m/z calcd for  $C_{21}H_{30}O_3$ : 330.2195; found: 330.2214 (Dev. 5.7 ppm).

Alkylation of Propionate Ester 3 in THF; General Procedure

The propionate ester 3 (1 equiv) was dissolved in THF (10 mL/ mmol) under argon and the reaction flask was cooled to -78 °C by immersion in a bath of dry ice-isopropyl alcohol. A solution of LDA in cyclohexane (1.2 equiv) was added slowly by syringe, and the reaction mixture was stirred at -78 °C for 2 h. The alkyl halide (5-10 equiv) was then added to the stirred solution slowly by syringe. After stirring at -78 °C for 6 h, the mixture was allowed to warm to r.t. with stirring for a further 18 h at r.t. The mixture was then diluted with  $Et_2O$  (15 mL/mmol) and  $H_2O$  (10 mL/mmol) at 0 °C. The  $Et_2O$ layer was extracted with 10% aq HCl ( $3 \times 30$  mL). The combined aqueous layers were saturated with NaCl, and extracted with Et2O  $(2 \times 20 \text{ mL})$ . The combined Et<sub>2</sub>O layers were washed with sat. aq NaHCO<sub>3</sub> ( $2 \times 25$  mL) and brine (40 mL), dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. Purification of the resultant oil by sequential column chromatography (90:10 hexane-EtOAc) and HPLC (95:5 hexane-EtOAc at 1 mL/min) yielded the product as a mixture of the diastereomeric 2-methylalkanoate esters

## Alkylation with Ethyl Bromide in THF; Isolation of Products 5a, 6a, 7a and 8

Alkylation of the ester **3** (0.840 g, 2.54 mmol) with ethyl bromide (2.77 g, 25.4 mmol) by the general procedure yielded three products. Column chromatography yielded two fractions. The polar fraction isolated by column chromatography was obtained as a colorless oil (0.02 g, 4%) consisting of a 1:1 mixture of the (R)- and (S)-methyl-3-oxopentanoic acid esters of **8**.

#### (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Esters of (*R*)-2-Methyl-3-oxopentanoic Acid and (*S*)-2-Methyl-3-oxopentanoic Acid (8) IR: 2948, 1714, 1542, 1458, 1250, 1181, 1035, 835 cm<sup>-1</sup>.

<sup>1</sup>H NMR: δ = 7.07 (d, 2 H, J = 8.4 Hz, Ar-H), 6.80 (d, 2 H, J = 8.4 Hz, C2-H), 4.53 (d, 1 H, J = 4.0 Hz, C2-H), 3.77 (s, 3 H, OCH<sub>3</sub>), 3.36 (q, 1 H, J = 7.0 Hz, C2<sup>'''</sup>-H; isomer A\*), 3.35 (q, 1 H, J = 7.0 Hz, C2<sup>'''</sup>-H; isomer B\*), 2.78 (dd, 1 H, J = 7.5, 13.6 Hz, C1'-H), 2.58 (dd, 1 H, J = 7.5, 13.6 Hz, C1'-H), 2.36 (complex, 2 H, C3-H, C4<sup>'''</sup>-H), 1.21, (d, 3 H, J = 7.0 Hz, α-CH<sub>3</sub>; isomer A\*), 1.20 (d, 3 H, J = 7.0 Hz, α-CH<sub>3</sub>; isomer B\*), 1.10–1.70 (complex, 5 H, C4-H, C5-H, C6-H), 1.01 (t, 3 H, J = 7.2 Hz, C5<sup>'''</sup>-H), 0.95 (s, 3 H, C10-H), 0.83 (s, 3 H, C9-H), 0.75 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 206.2 (ketone C=O), 170.1 (ester C=O; isomer A\*), 170.0 (ester C=O, isomer B\*), 157.8 (C4"), 133.0 (C1"), 129.6 (C2"), 113.7 (C3"), 86.6 (C2), 55.2 (OCH<sub>3</sub>), 52.7 (C2"'), 50.2 (C1; isomer A\*), 50.1 (C1; isomer B\*), 49.1 (C4), 48.32 (C3; isomer A\*), 48.30 (C3; isomer B\*), 47.8 (C7), 35.9 (C6), 34.8 (C4"''; isomer A\*); 34.6 (C4"''; isomer B\*), 34.0 (C5), 20.4 (C9), 20.2 (C1'), 19.3 (C8), 12.80 (α-CH<sub>3</sub>; isomer A\*), 12.79 (α-CH<sub>3</sub>; isomer B\*), 11.5 (C10), 7.7 (C5<sup>'''</sup>).

EIMS: m/z (%) = 386 (M<sup>+</sup>, 33), 344 (15), 273 (29), 272 (81), 257 (47), 256 (87), 161 (64), 160 (91), 135 (98), 134 (63), 121 (100).

HRMS-EI: m/z calcd for C<sub>24</sub>H<sub>34</sub>O<sub>4</sub>: 386.2457; found: 386.2458 (Dev. 0.3 ppm).

HPLC purification of the less polar fraction from column chromatography gave two fractions. The less polar material obtained by HPLC was a colorless oil (0.10 g, 11%) and identified as **7a**.

## (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 2-Ethyl-2-methylbutanoate (7a)

IR: 2952, 1723, 1614, 1513, 1460, 1300, 1248, 1150, 1039, 840, 702 cm<sup>-1</sup>.

<sup>1</sup>H NMR: δ = 7.04 (d, 2 H, *J* = 8.7 Hz, ArH), 6.79 (d, 2 H, *J* = 8.7 Hz, ArH), 4.46 (d, 1 H, *J* = 3.8 Hz, C2-H), 3.77 (s, 3 H, OCH<sub>3</sub>), 2.92 (dd, 1 H, *J* = 6.1, 13.7 Hz, C1'-H<sub>R</sub>), 2.57 (dd, 1 H, *J* = 10.0, 13.7 Hz, C1'-H<sub>5</sub>), 2.37 (complex, 1 H, C3-H), 1.10–1.7 (complex, 9 H, C4-H, C5-H, C6-H, C3'''-H), 1.02 (s, 3 H, α-CH<sub>3</sub>), 1.00 (s, 3 H, C10-H), 0.83 (s, 3 H, C9-H), 0.80 (t, 3 H, *J* = 7.4 Hz, CH<sub>3</sub>), 0.78 (t, 3 H, *J* = 7.4 Hz, CH<sub>3</sub>), 0.78 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 176.7 (C=O), 157.6 (C4''), 133.3 (Cl''), 129.5 (C2''), 113.7 (C3''), 85.3 (C2), 55.1 (OCH<sub>3</sub>), 49.7 (Cl), 49.6 (C4), 47.6 (C3), 46.5 (C7), 35.6 (C6), 34.1 (C5), 31.5 (C2'''), 31.3 (C3'''), 20.5 (C-9), 20.1 (C-1, α-CH<sub>3</sub>), 19.4 (C8), 11.8 (C10), 8.9 (C4''').

EIMS: m/z (%) = 386 (M<sup>+</sup>, 8), 272 (27), 262 (28), 256 (29), 231 (26), 160 (66), 149 (28), 135 (21), 121 (42), 109 (62).

HRMS-EI: m/z calcd for  $C_{25}H_{38}O_3$ : 386.2821; found: 386.2828 (Dev. 1.9 ppm).

The more polar material obtained by HPLC was a colorless oil (0.55 g, 60%) and identified as a 71:29 mixture **5a** and **6a**.

# (1R,2R,3S,4R)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Esters of (*R*)-2-Methylbutanoic Acid (5a) and (*S*)-2-Methylbutanoic Acid (6a)

IR: 2963, 1731, 1613, 1512, 1462, 1245, 1179, 1152, 1037, 835  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR: δ = 7.06 (d, 2 H, J = 8.5 Hz, ArH), 6.78 (d, 2 H, J = 8.5 Hz, ArH), 4.49 (d, 1 H, J = 4.0 Hz, C2-H), 3.75 (s, 3 H, OCH<sub>3</sub>), 2.82 (dd, 1 H, J = 7.5, 13.7 Hz, C1′-H<sub>5</sub>; S ester), 2.81 (dd, 1 H, J = 7.5, 13.7 Hz, C1′-H<sub>5</sub>; S ester), 2.81 (dd, 1 H, J = 7.5, 13.7 Hz, C1′-H<sub>5</sub>; R ester), 2.57 (dd, 1 H, J = 8.4, 13.6 Hz, C1′-H<sub>R</sub>), 2.37 (complex, 1 H, C3-H), 2.22 (sextet, 1 H, J = 7.0 Hz, C2″′′-H), 1.10–1.7 (complex, 7 H, C4-H, C5-H, C6-H, C3″′-H), 1.03 (d, 3 H, J = 6.9 Hz,  $\alpha$ -CH<sub>3</sub> S ester), 1.00 (s, 3 H, C10-H), 0.834 (t, 3 H, J = 7.5 Hz, CH<sub>3</sub>), 0.83 (s, 3 H, C9-H), 0.75 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 176.0 (C=O), 157.9 (C4″), 133.4 (C1″), 129.6 (C2″), 113.7, (C3″″), 85.1 (C2), 55.0 (OCH<sub>3</sub>), 49.7 (Cl), 49.1 (C4), 48.0 (C7), 47.5 (C3), 41.3 (C2″'), 35.7 (C6), 33.9 (C5), 26.4 (C3″'), 20.2 (C9), 19.9 (C1′), 19.2 (C8), 16.3 (α-CH<sub>3</sub>), 11,3 (C10, C4″).

EIMS: *m*/*z* (%) = 358 (M<sup>+</sup>, 28), 257 (10), 256 (47), 252 (14), 167 (15), 161 (33), 160 (85) 123 (58), 121 (62), 69 (62), 57 (100).

HRMS-EI: m/z calcd for  $C_{25}H_{34}O_3$ : 358.2508; found: 358.2513 (Dev. 1.5 ppm).

## Alkylation with *n*-Butyl Bromide; Isolation of Products 5b, 6b, and 7b

The alkylation of the ester **3** (0.555 g, 1.68 mmol) with 1-bromobutane (2.301 g, 16.8 mmol) by the general procedure yielded two alkylation products which were separated by HPLC.

The more polar material was a colorless oil (0.42 g, 65%) identified as a 71:29 mixture of **5b** and **6b**.

#### (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Esters of (*R*)-2-Methylhexanoic Acid (5b) and (*S*)-2-Methylhexanoic Acid (6b)

IR: 2948, 1731, 1613, 1513, 1461, 1248, 1178, 1038, 837 cm<sup>-1</sup>.

<sup>1</sup>H NMR: δ = 7.05 (d, 2 H, J = 8.6 Hz, ArH), 6.77 (d, 2 H, J = 8.6 Hz, ArH), 4.49 (d, 1 H, J = 4.0 Hz, C2-H), 3.74 (s, 3 H, OCH<sub>3</sub>), 2.82 (dd, 1 H, J = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *S* ester), 2.81 (dd, 1 H, J = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *R* ester), 2.81 (dd, 1 H, J = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *R* ester), 2.81 (dd, 1 H, J = 7.4, 2.31 (complex, 1 H, C3-H), 2.26 (sextet, 1 H, J = 7.2 Hz, C2'''-H), 1.10–1.7 (complex, 7 H, C4-H, C5-H, C6-H, C3'''-H), 1.03 (d, 3 H, J = 7.0 Hz, α-CH<sub>3</sub>; *S* ester), 1.004 (d, 3 H, J = 6.9 Hz, α-CH<sub>3</sub>; *R* ester), 1.00 (s, 3 H, C10-H), 0.87 (t, 3 H, J = 6.3 Hz, CH<sub>3</sub>), 0.83 (s, 3 H, C9-H), 0.76 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 175.9 (C=O), 157.7 (C4"), 133.2 (Cl"), 129.5 (C2"), 113.7 (C3"), 85.4 (C2), 55.1 (OCH<sub>3</sub>), 49.9 (Cl), 49.3 (C4), 48.2 (C3), 47.7 (C7), 39.9 (C2"), 35.9 (C6), 34.1 (C5), 33.3 (C3"'), 29.4 (C4"'), 22.6 (C5"'), 20.4 (C9), 20.2 (C1'), 19.4 (C8), 17.1 (α-CH<sub>3</sub>), 13.9 (C6″''), 11.6 (C10).

EIMS: *m*/*z* (%) = 386 (M<sup>+</sup>, 31), 256 (100), 161 (45), 160 (91), 159 (12), 134 (12), 122 (20), 121 (65), 85 (21).

HRMS-EI: m/z calcd for  $C_{25}H_{38}O_3$ : 386.2821; found: 386.2824 (Dev. 0.9 ppm).

The less polar material obtained by HPLC was a colorless oil (0.03 g, 4%) identified as **7b**.

## (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl 2-butyl-2-methyl Hexanoate (7b)

IR: 2949, 1725, 1614, 1512, 1465, 1249, 1205, 1178, 1151, 1040, 976, 838, 701 cm<sup>-1</sup>.

<sup>1</sup>H NMR:  $\delta$  = 7.04 (d, 2 H, *J* = 8.5 Hz, ArH), 6.79 (d, 2 H, *J* = 8.5 Hz, ArH), 4.44 (d, 1 H, *J* = 3.7 Hz, C2-H), 3.77 (s, 3 H, OCH<sub>3</sub>), 2.96 (dd, 1 H, *J* = 5.5, 13.8 Hz, C1'-H<sub>s</sub>), 2.56 (dd, 1 H, *J* = 10.4, 13.7 Hz, C1'-H<sub>R</sub>), 2.31 (complex, 1 H, C3-H), 1.10–1.70 (complex, 17 H, C4-H, C5-H, C6-H, C3'''-H, C4'''-H, C5'''-H), 1.05 (s, 3 H, CH<sub>3</sub>), 0.99 (s, 3 H, C10-H), 0.88 (t, 3 H, *J* = 6.9 Hz, CH<sub>3</sub>), 0.83 (s, 3 H, C9-H), 0.78 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 177.0 (C=O), 157.6 (C4'), 133.4 (Cl''), 129.5 (C2''), 113.6 (C3''), 85.4 (C2), 55.2 (OCH<sub>3</sub>), 49.7(C4), 49.67 (C2'''), 47.6 (Cl), 47.4 (C3), 45.8 (C7), 39.3 (C3'''), 35.4 (C6), 34.1 (C5), 26.8 (C4'''), 23.3 (C5'''), 21.1 (α-CH<sub>3</sub>), 20.5 (C9), 20.1 (C1'), 19.4 (C8), 14.1 (C6'''), 11.8 (C10).

EIMS: m/z (%) = 442 (M<sup>+</sup>, 4), 256 (10), 210 (61), 168 (40), 105 (36), 91 (100).

HRMS-EI: m/z calcd for  $C_{29}H_{46}O_3$ : 442.3447; found: 442.3458 (Dev. 2.6 ppm).

## Alkylation with Isopropyl Bromide; Isolation of Products 5c and 6c

The alkylation of the ester **3** (1.24 g, 3.64 mmol) with isopropyl bromide (4.482 g, 36.4 mmol) by the general procedure yielded one monoalkylation product which was purified by HPLC to give a colorless oil (0.34 g, 25%) identified as a 70:30 mixture of **5c** and **6c**, respectively.

#### (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Esters of (*R*)-2,3-Dimethylbutanoic Acid (5c) and (*S*)-2,3-Dimethylbutanoic Acid (6c) IP: 2961–1730–1513–1249–1170–1041–838 cm<sup>-1</sup>

IR: 2961, 1730, 1513, 1249, 1179, 1041, 838 cm<sup>-1</sup>.

<sup>1</sup>H NMR:  $\delta$  = 7.05 (d, 2 H, *J* = 8.4 Hz, ArH), 6.77 (d, 2 H, *J* = 8.4 Hz, ArH), 4.50 (d, 1 H, *J* = 3.9 Hz, C2-H), 3.74 (s, 3 H, OCH<sub>3</sub>), 2.83 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H), 2.57 (dd, 1 H, *J* = 8.8, 13.6 Hz, C1'-H), 2.36 (complex, 1 H, C3-H), 2.08 (sextet, I H, *J* = 7.0 Hz, C2'''-H), 1.82 (octet, 1 H, *J* = 7.0 Hz, C3'''-H), 1.10–1.7 (complex,

5 H, C4-H, C5-H, C6-H), 1.02 (d, 3 H, J = 7.0 Hz,  $\alpha$ -CH<sub>3</sub>; S ester), 1.00 (d, 3 H, J = 6.9 Hz,  $\alpha$ -CH<sub>3</sub>; R ester), 1.00 (s, 3 H, C10-H), 0.85 (d, 3 H, J = 6.7 Hz, CH<sub>3</sub>), 0.84 (d, 3 H, J = 6.7 Hz, CH<sub>3</sub>), 0.82 (s, 3 H, C9-H), 0.77 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 175.4 (C=O), 157.7 (C4<sup>''</sup>), 133.2 (Cl<sup>''</sup>), 129.5 (C2<sup>''</sup>), 113.7 (C3<sup>''</sup>), 85.1 (C2), 55.1 (OCH<sub>3</sub>), 49.9 (Cl), 49.3 (C4), 48.1 (C3), 47.7 (C7), 46.8 (C2<sup>'''</sup>), 35.9 (C6), 34.1 (C5), 30.7 (C3<sup>'''</sup>), 20.8 (α-CH<sub>3</sub>), 20.4 (C9), 20.2 (C1<sup>'</sup>), 19.4 (C8), 19.0 (C4<sup>'''</sup>), 13.7 (C4<sup>'''</sup>), 11.8 (C10).

EIMS: *m*/*z* (%) = 372 (M<sup>+</sup>, 13), 256 (59), 161 (17), 160 (100), 122 (11), 121 (67).

HRMS-EI: m/z calcd for  $C_{24}H_{36}O_3$ : 372.2665; found: 372.2687 (Dev. 6.0 ppm).

## Alkylation with Cyclopentyl Bromide; Isolation of Products 5d and 6d

The alkylation of the ester **3** (0.806 g, 2.44 mmol) with cyclopentyl bromide (1.818 g, 12.2 mmol) by the general procedure yielded one monoalkylation product which was purified by HPLC to give a colorless oil (0.25 g, 26%) identified as a 67:33 mixture of **5d** and **6d**, respectively.

#### (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Esters of (*R*)-2-Cyclopentylpropanoic Acid (5d) and (*S*)-2-Cyclopentylpropanoic Acid (6d)

IR: 2955, 1729, 1613, 1512, 1457, 1249, 1155, 1040, 838 cm<sup>-1</sup>.

<sup>1</sup>H NMR: δ = 7.06 (d, 2 H, *J* = 8.6 Hz, ArH), 6. 78 (d, 2 H, *J* = 8.6 Hz, ArH), 4.50 (d, 1 H, *J* = 4.0 Hz, C2-H), 3.75 (s, 3 H, OCH<sub>3</sub>), 2.82 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *S* ester), 2.81 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *R* ester), 2.81 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *R* ester), 2.57 (dd, 1 H, *J* = 8.8, 13.6 Hz, C1'-H<sub>R</sub>), 2.36 (complex, 1 H, C3-H), 2.11 (complex, 1 H, C2'''-H), 1.10–2.0 (complex, 14 H, C4-H, C5-H, C6-H, C3'''-H, C4'''-H, C5'''-H), 1.03 (d, 3 H, *J* = 7.0 Hz, α-CH<sub>3</sub>; *S* ester), 1.00 (d, 3 H, *J* = 6.9 Hz, α-CH<sub>3</sub>: *R* ester), 1.00 (s, 3 H, C10-H), 0.83 (s, 3 H, C9-H), 0.77 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 175.8 (C=O), 157.7 (C4''), 133.3 (Cl''), 129.5 (C2''), 113.7 (C3''), 85.1 (C2), 55.2 (OCH<sub>3</sub>), 49.9 (Cl), 49.3 (C4), 48.2 (C3), 47.7 (C7), 45.8 (C2'''), 43.1(C3'''), 36.0 (C-6), 34.1 (C5), 31.0 (C4<sub>a</sub>'''), 30.2 (C4<sub>b</sub>'''), 25.2 (C5'''), 20.4 (C-9), 20.2 (C-1'), 19.4 (C-8), 16.3 (α-CH<sub>3</sub>), 11.7 (C-10).

EIMS: *m*/*z* (%) = 398 (M<sup>+</sup>, 29), 256 (100), 161 (45), 160 (95), 159 (13), 135 (11), 134 (13), 122 (23), 121 (74), 97 (37).

HRMS-EI: m/z calcd. for  $C_{26}H_{38}O_3$ : 398.2821; found: 398.2833 (Dev. 3.1 ppm).

Alkylation with Isobutyl Iodide; Isolation of Products 5e and 6e The alkylation of the ester 3 (0.797 g, 2.41 mmol) with isobutyl iodide (4.434 g, 24.1 mmol) by this procedure yielded one monoalkylation product which was purified by HPLC to give a colorless oil (0.22 g, 23%) identified as a 63:37 mixture of 5e and 6e, respectively.

#### (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Esters of (*R*)-2,3-Dimethylpentanoic Acid (5e) and (*S*)-2,3-Dimethylpentanoic Acid (6e)

IR: 2957, 1731, 1613, 1513, 1461, 1247, 1177, 1152, 1038, 837 cm<sup>-1</sup>.

<sup>1</sup>H NMR:  $\delta$  = 7.06 (d, 2 H, *J* = 8.7 Hz, ArH), 6.78 (d, 2 H, *J* = 8.7 Hz, ArH), 4.48 (d, 1 H, *J* = 4.0 Hz, C2-H), 3.76 (s, 3 H, OCH<sub>3</sub>), 2.82 (dd, 1 H, *J* = 7.5, 13.6 Hz, Cl'-H<sub>5</sub>; *S* ester), 2.79 (dd, 1 H, *J* = 7.5, 13.6 Hz, Cl'-H<sub>5</sub>; *R* ester), 2.57 (dd, 1 H, *J* = 8.8, 13.6 Hz, C1'-H<sub>R</sub>), 2.36 (complex, 1 H, C3-H), 2.27 (sextet, 1 H, *J* = 7.6 Hz, C2'''-H), 1.10–1.7 (complex, 8 H, C4-H, C5-H, C6-H, C3'''-H, C4'''-H), 1.02 (d, 3 H, *J* = 7.0 Hz, α-CH<sub>3</sub>; *S* ester), 1.00 (d, 3 H, *J* = 6.9 Hz, α-CH<sub>3</sub>;

*R* ester), 1.00 (s, 3 H, C10-H), 0.86 (d, 3 H, J = 6.5 Hz, CH<sub>3</sub> [*i*-Pr]), 0.84 (d, 3 H, J = 6.1 Hz, CH<sub>3</sub> [*i*-Pr]), (0.82 (s, 3 H, C9-H), 0.76 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 176.1 (C=O), 157.7 (C4″), 133.3 (Cl″), 129.5 (C2″), 113.6 (C3″), 85.1 (C2), 55.2 (OCH<sub>3</sub>), 49.9 (Cl), 49.3 (C4), 48.2 (C3), 47.7 (C7), 43.0 (C2″'), 38.1 (C4″'), 35.9 (C6), 34.1 (C5), 25.8 (C3″'), 22.7 (α-CH<sub>3</sub>), 22.3 (C5″'), 20.4 (C9), 20.2 (C1′), 19.4 (C8), 17.6 (C5″''), 11.6 (C10).

EIMS: *m*/*z* (%) = 386 (M<sup>+</sup>, 6), 256 (39), 161 (14), 160 (100), 122 (11), 121 (62).

HRMS-EI: m/z calcd for  $C_{25}H_{38}O_3$ : 386.2821; found: 386.2817 (Dev. 0.9 ppm).

Alkylation with Allyl Chloride; Isolation of Products 5f and 6f The alkylation of the ester 3 (0.676 g, 2.04 mmol) with allyl chloride (1.564 g, 20.4 mmol) by this procedure yielded one monoalkylation product which was purified by HPLC to give a colorless oil (0.35 g, 46%) identified as a 70:30 mixture of 5f and 6f, respectively.

# 1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Esters of (*R*)-2-Methylpent-4-enoic Acid (5f) and (*S*)-2-Methylpent-4-enoic Acid (6f)

IR: 2954, 1733, 1613, 1515, 1460, 1249, 1180, 1040, 916, 836 cm<sup>-1</sup>.

<sup>1</sup>H NMR: δ = 7.06 (d, 2 H, *J* = 8.6 Hz, ArH), 6.78 (d, 2 H, *J* = 8.6 Hz, ArH), 5.70 (ddt, 1 H, *J* = 6.8, 10.2, 17.2 Hz, C4<sup>'''</sup>-H), 5.02 (dd, 1 H, *J* = 1.0, 17.2 Hz, C5<sup>'''</sup>-H<sub>trans</sub>), 5.00 (dd, 1 H, *J* = 1.0, 10.2 Hz, C5<sup>'''</sup>-H<sub>cis</sub>), 4.48 (d, 1 H, *J* = 4.0 Hz, C2-H), 3.74 (s, 3 H, OCH<sub>3</sub>), 2.81 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *S* ester), 2.79 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *R* ester), 2.56 (dd, 1 H, *J* = 8.8, 13.6 Hz, C1'-H<sub>R</sub>), 2.37 (complex, 1 H, C3-H), 2.26 (complex, 2 H, C3'''-H), 2.06 (sextet, 1 H, *J* = 6.8 Hz, C2'''-H), 1.10–1.7 (complex, 5 H, C4-H, C5-H, C6-H), 1.03 (d, 3 H, *J* = 7.0 Hz, *a*-CH<sub>3</sub>; *S* ester), 1.00 (d, 3 H, *J* = 6.9 Hz, *a*-CH<sub>3</sub>; *R* ester), 1.00 (s, 3 H, C10-H), 0.82 (s, 3 H, C9-H), 0.75 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 175.1 (C=O), 157.7 (C4''), 135.7 (C4''') 133.2 (Cl''), 129.5 (C2''), 116.6 (C5'''), 113.7 (C3''), 85.4 (C2), 55.1 (OCH<sub>3</sub>), 49.9 (Cl), 49.2 (C4), 48.1 (C3), 47.7 (C7), 39.6 (C2'''), 37.7 (C3'''), 35.8 (C6), 34.0 (C5), 20.4 (C9), 20.2 (Cl'), 19.4 (C8), 16.5 (α-CH<sub>3</sub>), 11.6 (C10).

EIMS: *m*/*z* (%) = 370 (M<sup>+</sup>, 15), 256 (52), 161 (16), 160 (100), 122 (10), 121 (59).

HRMS-EI: m/z calcd for C<sub>24</sub>H<sub>34</sub>O<sub>3</sub>: 370.2508; found: 370.2523 (Dev. 4.1 ppm).

## Alkylation with Methallyl Chloride; Isolation of Products of 5g and 6g

The alkylation of the ester **3** (0.714 g, 2.16 mmol) with methallyl chloride (1.956 g, 21.6 mmol) by this procedure yielded one monoalkylation product, which was purified by HPLC to give a colorless oil (0.35 g, 42%) and identified as a 71:29 mixture of the **5g** and **6g**, respectively.

# (1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl Esters of (*R*)-2,4-Dimethylpent-4-enoic Acid (5g) and (*S*)-2,4-Dimethylpent-4-enoic Acid (6g) IR: 2961, 1734, 1513, 1461, 1250, 1180, 1041, 895, 839 cm<sup>-1</sup>.

<sup>1</sup>H NMR:  $\delta$  = 7.06 (d, 2 H, *J* = 8.6 Hz, ArH), 6.78 (d, 2 H, *J* = 8.6 Hz, ArH), 4.76 (s, 1 H, =CH<sub>2</sub>), 4.69 (s, 1 H, =CH<sub>2</sub>), 4.47 (d, 1 H, *J* = 4.0 Hz, C2-H), 3.75 (s, 3 H, OCH<sub>3</sub>), 2.83 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *S* ester), 2.81 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H<sub>5</sub>; *R* ester), 2.57 (dd, 1 H, 5 = 8.8, 13.6 Hz, C1'-H<sub>R</sub>), 2.50 (d, 1 H, *J* = 7.0 Hz, C3'''-H), 2.36 (complex, 1 H, C3-H), 2.29 (sextet, 1 H, *J* = 7.6 Hz, C2'''-H), 1.96 (dd, 1 H, *J* = 7.4 Hz, C3'''-H), 1.69 (s, 3 H, γ-CH<sub>3</sub>),

1.10–1.68 (complex, 5 H, C4-H, C5-H, C6-H), 1.03 (d, 3 H, J = 7.0 Hz,  $\alpha$ -CH<sub>3</sub>; S ester), 1.004 (d, 3 H, J = 6.8 Hz,  $\alpha$ -CH<sub>3</sub>; R ester), 1.00 (s, 3 H, C10-H), 0.83 (s, 3 H, C9-H), 0.75 (s, 3 H, C8-H).

<sup>13</sup>C NMR: δ = 175.5 (C=O), 157.7 (C4″), 142.9 (C4″'), 133.3 (Cl″), 129.5 (C2″), 113.7 (C3″), 112.1 (C5″'), 85.4 (C2), 55.2 (OCH<sub>3</sub>), 49.9 (Cl), 49.2 (C4), 48.0 (C3), 47.7 (C7), 41.9 (C3″'), 38.1 (C2″'), 35.7 (C6), 34.0 (C5), 22.2 (γ-CH<sub>3</sub>), 20.4 (C9), 20.1 (C1′), 19.4 (C8), 16.8 (α-CH<sub>3</sub>), 11.6 (C10).

EIMS: m/z (%) = 384 (M<sup>+</sup>, 9), 256 (81), 161 (13), 160 (95), 122 (16), 121 (100), 83 (20).

HRMS-EI: m/z Found: 384.2687. Calcd for  $C_{25}H_{30}O_3$ : 384.2665 (Dev. 5.9 ppm).

Alkylation of Propionate Ester 3 with Ethyl Bromide in THF-HMPA; Reversal of Stereochemistry of the Products 5a and 6a The propionate ester 3 (0.772 g, 2.34 mmol) was dissolved in THF (15 mL) and HMPA (4.5 mL), and the reaction flask was then cooled to -78 °C by immersion in a bath of dry ice-iPrOH. The LDA solution (1.2 equiv) was added slowly by syringe and the reaction mixture was stirred at -78 °C for 2 h. Ethyl bromide (2.546 g, 23.4 mmol) was then added slowly to the stirred solution by syringe. After stirring a further 6 h at -78 °C, the mixture was allowed to warm to r.t. and stirred for 18 h. The mixture was then diluted with Et<sub>2</sub>O (30 mL) and H<sub>2</sub>O (10 mL) at 0 °C. The Et<sub>2</sub>O layer was extracted with dil. HCl ( $3 \times 30$  mL). The combined aqueous layers were saturated with NaCl, and extracted with  $Et_2O(2 \times 20 \text{ mL})$ . The combined Et<sub>2</sub>O layers were washed with sat. aq NaHCO<sub>3</sub> (2  $\times$  25 mL) and brine (40 mL), dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. Purification of the product by column chromatography (90:10 hexane-EtOAc) and HPLC (95:5 hexane-EtOAc at 1 mL/min) yielded the monoalkylation product as a colorless oil (0.50 g, 60%) consisting of a 38:62 mixture of **5a** and **6a**, respectively. Chemical shifts of the <sup>1</sup>H NMR and <sup>13</sup>C NMR resonances were identical to those of the product of alkylation in THF alone.

# (1R,2R,3S,4R)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl (S)-2-Methylbutanoate (6a) by Direct Esterification of 1 with (S,S)-2-Methylbutanoic Anhydride

A solution of 1 (1.77 g, 6.44 mmol) in THF (5 mL) was added dropwise to a stirred suspension of NaH (60% dispersion in oil, 0.309 g, 1.2 equiv) in anhyd THF (10 mL) at -20 °C. After 30 min, (*S*,*S*)-(+)-2-methylbutanoic anhydride (1.00 g, 5.37 mmol) in anhyd THF (2 mL) was added to the reaction mixture. The mixture was stirred at -20 °C for 1 h and then stirred at r.t. for 3 d. The mixture was then cooled in ice and diluted with Et<sub>2</sub>O (30 mL) and H<sub>2</sub>O (20 mL). The Et<sub>2</sub>O layer was separated and washed once with H<sub>2</sub>O (30 mL). The organic layer was washed sequentially with sat. aq NaHCO<sub>3</sub> (3 ´ 30 mL), H<sub>2</sub>O (30 mL), and brine (30 mL), dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. Purification of the product by column chromatography (90:10 hexane–EtOAc) yielded the product as a colorless oil (0.67 g, 35%).

IR: 2962, 1730, 1613, 1513, 1465, 1254, 1183, 1043, 840 cm<sup>-1</sup>.

<sup>1</sup>H NMR: δ = 7.06 (d, 2 H, *J* = 8.5 Hz, ArH), 6.78 (d, 2 H, *J* = 8.5 Hz, ArH), 4.48 (d, 1 H, *J* = 4.0 Hz, C2-H), 3.75 (s, 3 H, OCH<sub>3</sub>), 2.82 (dd, 1 H, *J* = 7.3, 13.6 Hz, C1'-H<sub>s</sub>), 2.57 (dd, 1 H, *J* = 8.5, 13.6 Hz, C1'-H<sub>R</sub>), 2.36 (complex, 1 H, C3-H), 2.23 (sextet, 1 H, *J* = 6.9 Hz, C2'''-H), 1.10–1.70 (complex, 7 H, C4-H, C5-H, C6-H, C3'''-H), 1.03 (t, 3 H, *J* = 7.0 Hz, α-CH<sub>3</sub>), 1.00 (s, 3 H, C10-H), 0.84 (t, 3 H, *J* = 7.4 Hz, C4'''-H), 0.83 (s, 3 H, C9-H), 0.76 (s, 3 H, C8-H).

<sup>13</sup>C NMR: d = 175.9 (C=O), 157.7 (C4''), 133.3 (Cl''), 129.5 (C2''), 113.7 (C3''), 85.2 (C2), 55.2 (OCH<sub>3</sub>), 49.9 (Cl), 49.2 (C4), 48.1(C3), 47.7 (C7), 41.4 (C2'''), 35.8 (C6), 34.1 (C5), 26.6 (C3'''), 20.4 (C9), 20.2 (C1'), 19.4 (C8), 16.7 (α-CH<sub>3</sub>), 11.6 (C10, C4''').

EIMS: m/z (%) = 358 (M<sup>+</sup>, 9), 256 (20), 220 (54), 205 (44), 136 (50), 135 (52), 121 (74), 112(71), 85 (100).

HRMS-EI: m/z calcd for C<sub>23</sub>H<sub>34</sub>O<sub>3</sub>: 358.2508; found: 358.2525 (Dev. 4.7 ppm).

#### 1*R*,2*R*,3*S*,4*R*)-3-[(4-Methoxyphenyl)methyl]-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl (*R*)-2-Methylbutanoate (5a) and (*S*)-2-Methylbutanoate (6a) by Direct Esterification of 1 with the Racemic 2-Methylbutyryl Chloride

Racemic 2-methylbutyric acid (2.04 g, 20 mmol) in anhyd THF (2 mL) was added to a stirred suspension of NaH (60% dispersion in oil, 0.96 g, 24 mmol) in anhyd THF (30 mL). After 30 min, POCl<sub>3</sub> (0.92 g, 6.0 mmol) was added by syringe. The reaction mixture was stirred for 1 h and a solution of **1** (1.0 equiv, 2.74 g, 10.0 mmol) in THF (5 mL) was added. The mixture was stirred 3 d at r.t., then diluted with  $H_2O$  (20 mL) and extracted with  $H_2O$  (50 mL). The organic extract was washed sequentially with sat. aq NaHCO<sub>3</sub> (50 mL) and brine (50 mL), dried (MgSO<sub>4</sub>), and evaporated under reduced pressure to give a colorless oil (4.15 g, 58%).

<sup>1</sup>H NMR: δ = 2.81 (dd, 1 H, J = 7.3, 13.6 Hz, C1'-H<sub>s</sub>, S ester), 2.80 (dd, 1 H, J = 7,6, 13.6, C1'-H<sub>s</sub>, R ester).

## Acknowledgments

This work was supported in part by funds from the South Dakota State University Research Support Fund.

### References

- Current address: Department of Chemistry, University of Wisconsin - Eau Claire, Eau Claire, WI 54702-4004, USA, e-mail: lewisd@uwec.edu.
- (2) Reviews: (a) Caine, D. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M., Ed.; Pergamon: Oxford, **1991**, 1–63. (b) Evans, D. A. In *Asymmetric Synthesis*, Vol. 3; Morrison, J. D., Ed.; Academic Press: Orlando/FL, **1984**, Chap. 1, 1–110. (c) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (d) For explicit use of bornane-based esters in alkylation, see: Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212.
- (3) (a) Seo, B.-I.; Suh, I.-H.; Jensen, W. P.; Lewis, D. E.; Wall, L. K.; Jacobson, W. P. *Tetrahedron: Asymmetry* **1992**, *3*, 367. (b) Suh, I.-H.; Seo, B.-I.; Lewis, D. E.; Jensen, W. P.; Jacobson, R. A. *Acta Crystallogr., Sect. C* **1993**, *C43*, 562.
- (4) (a) Seo, B.-I.; Wall, L. K.; Lee, H.; Buttrum, J.; Lewis, D. E. Synth. Commun. 1993, 23, 15. (b) Richer, J.-C.; Rossi, A. Can. J. Chem. 1972, 50, 1376. (c) Wall, L. K. MS Thesis; Baylor University: USA, 1990.
- (5) Montgomery, S. H.; Pirrung, M. C.; Heathcock, C. H. Org. Synth. 1984, 63, 99.
- (6) Ireland, R. E.; Muller, R. H.; Eilhard, A. K. J. Am. Chem. Soc. 1976, 98, 2868.
- (7) Munchhof, M. J.; Heathcock, C. H. *Tetrahedron Lett.* 1992, 33, 8005.