Oxidation of Diols and Ethers by NaBrO₃/NaHSO₃ Reagent

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NaBrO₃ combined with NaHSO₃ was found to be an excellent oxidizing reagent of alcohols, diols, and ethers under mild conditions. A variety of aliphatic and cyclic diols were selectively oxidized with satisfactory yields to the corresponding hydroxy ketones and/or diketones, which are difficult to selectively prepare due to a concomitant formation of cleaved products. For example, 2-hydroxycyclohexanone and 1,2-cyclohexanedione were selectively formed by allowing 1,2-cyclohexanediol to react with NaBrO₃/NaHSO₃ reagent in a selected solvent. On the other hand, an alkyl ether, such as dioctyl ether, reacted with NaBrO₃/NaHSO₃ in water at room temperature to give octyl octanoate in 82% yield. The same oxidation at higher temperature (60 °C) produced the α-brominated ester, octyl 2-bromo octanoate, which is considered to be formed through an alkenyl alkyl ether as the intermediate. The treatment of 1-ethoxy-1-heptene with NaBrO₃/NaHSO₃ afforded ethyl 2-bromoheptanoate and 2-bromoheptanoic acid as the major products.

The oxidative dehydrogenation of alcoholic functions to carbonyl ones and the oxidation of ethers to esters are common transformations in organic synthesis. Therefore, a number of methods have been developed for this purpose. Although sodium bromite (NaBrO₂) can oxidize alcohols to ketones, and α,ω-diols to lactones, the reagent is difficult to prepare. Sodium bromate, NaBrO₃, is used as an oxidant for RuCl₃- and cerium ammonium nitrate (CAN)-catalyzed oxidations of alcohols and esters. In addition, it is reported that it serves as the effective oxidant of alcohols, ethers, and silyl ethers in the presence of Lewis acids, HBr, and Br₂. In a previous paper, we showed that NaBrO₃ in combination with an appropriate reducing agent, such as NaHSO₃, generates in situ hypobromous acid, BrOH, and acts as a prominent reagent for the bromohydroxylation of alkenes (Eq. 1). In addition, 'NaBrO₃/NaHSO₃ reagent', which is a mixture of equimolar amounts of NaBrO₃ and NaHSO₃, oxidized primary alcohols to esters, and α,ω-diols to dicarboxylic acids or lactones in aqueous medium under mild conditions.

\[
\begin{align*}
\text{R}^1\text{C}(-\text{OH})\text{CH}_2\text{CHR}^2 & \quad \text{NaBrO}_3 / \text{NaHSO}_3 \\
\text{CH}_3\text{CN/H}_2\text{O, r.t.} & \quad \text{OH} \\
\text{R}^1\text{Br} & \quad \text{R}^2 \quad \text{Br} \\
\end{align*}
\]

In this paper, we wish to report on the application of NaBrO₃/NaHSO₃ reagent for the selective oxidation of various diols to α-hydroxy ketones and/or diketones, and ethers to esters under mild conditions.

Results

Oxidation of Diols. Since α-hydroxy ketones are of value as intermediates in organic synthesis, these compounds have been prepared from a variety of substrates such as esters, enolates, epoxides, ketones, and alkenes. The direct oxidation of vic-diols, which are easily available from alkenes, is one of the most useful candidates for the synthesis of α-hydroxy ketones and 1,2-diketones. However, the oxidation of vic-diols to α-hydroxy ketones or 1,2-diketones using conventional methods is difficult to carry out due to the formation of undesired cleavage products, such as carboxylic acids and aldehydes. Therefore, the conversion of vic-diols to the corresponding carbonyl compounds is of interest from a synthetic point of view. Kajigaeshi et al. reported that NaBrO₃ combined with HBr is an excellent reagent for the oxidation of alcohols to carbonyl compounds, but no oxidation has been examined for vic-diols.

We first examined the oxidation of 1,2-cyclohexanediol (1) with NaBrO₃/NaHSO₃ under various reaction conditions (Table 1, Runs 1—3). The oxidation was achieved by adding dropwise an aqueous NaHSO₃ solution over a period of 0.5 h to a mixture of 1 and NaBrO₃ (1.2 molar amount with respect to 1) in aqueous acetonitrile at room temperature to give 2-hydroxy-1-cyclohexanone (2) in 95% yield (Run 1), although the oxidation of vic-diols with IO₄⁻ resulted in a cleavage of the carbon–carbon bond. When a NaHSO₃ solution was added all at once to the NaBrO₃ solution, the yield of 2 lowered to 51% (Run 2). To obtain 1,2-cyclohexanedione (3), 1 was oxidized under several conditions. The best result was obtained by the oxidation of 1 with 1.2 molar amount of NaBrO₃ and NaHSO₃ (NaBrO₃/NaHSO₃) reagent in a mixed solvent of CH₃CN/CH₂Cl₂ to give 3 in 74% yield (Run 3). To our best knowledge this is the practical example for the oxidation of 1 to 3 with high selectivity.

The treatment of 1, 2-cyclooctanediol (5) with NaBrO₃/NaHSO₃ under these conditions afforded 2-hydroxy-1,2-cyclooctanone (6) in high yield.
Table 1. Oxidation of Various vic-Diols by NaBrO₃/NaHSO₄<sup>a</sup>)

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Product (yield/%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>1</td>
<td>2(51) 3(19) COOH (18)</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>1</td>
<td>2(8) 3(74)</td>
</tr>
<tr>
<td>4&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>1</td>
<td>2(8) 3(74)</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;)</td>
<td>1</td>
<td>2(8) 3(74)</td>
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<td>8</td>
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<td>9</td>
<td></td>
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</tr>
<tr>
<td>10&lt;sup&gt;f&lt;/sup&gt;)</td>
<td>1</td>
<td>2(51) 3(19) COOH (18)</td>
</tr>
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</table>

<sup>a</sup>) To a solution of diol (5 mmol) and NaBrO₃ (6 mmol) in CH₃CN/H₂O (10/3 mL) was added dropwise NaHSO₄ (6 mmol) in H₂O (6 mL) during a period of 30 min at room temperature under stirring for 2 h.  
<sup>b</sup>) NaHSO₄ solution was added all at once.  
<sup>c</sup>) Diol (3 mmol) was allowed to react in CH₃CN/CH₂Cl₂/H₂O (6/3/5.4 mL) for 3 h.  
<sup>d</sup>) 6 h.  
<sup>e</sup>) Each 2.4 molar amounts of NaBrO₃ and NaHSO₄ with respect to substrate was used.  
<sup>f</sup>) Diol (2.5 mmol) was used.

ethanediol (17) with 1.2 molar amount of NaBrO₃/NaHSO₄ gave hydroxy ketone 18. Upon treatment of 17 with 2.4 molar amounts of NaBrO₃/NaHSO₄, 18 was obtained as the major product (80%) (Run 10).

Table 2 shows the oxidation of various diols using the NaBrO₃/NaHSO₄ reagent. When 1,3-cyclohexanediol (19) was treated with 1.2 molar amount of NaBrO₃/NaHSO₄, 2-cyclohexeneone (21) was obtained rather than 3-hydroxy-1-cyclohexanone (20) as the major product (80%) (Run 1). Although 19 was allowed to react with excess NaBrO₃/NaHSO₄ (3.6 molar amounts) to prepare 1,3-cyclohexanediene, undesired 2-bromo-1,3-cyclohexanediene (22) was formed in 71% yield (Run 2). The reaction path for the formation of 22 will be discussed later. 1,4-Cyclohexanediol (23) was converted into 4-hydroxycyclohexanone (24) and 1,4-cyclohexanediene (25) with 1.2 molar amount and 2.4 molar amounts of NaBrO₃/NaHSO₄, respectively, in good yields (Runs 3 and 4). The oxidation of 2,5-hexanediol (28) with NaBrO₃/NaHSO₄ (2.4 molar amounts) produced 2,5-hexanedicone (29) in almost quantitative yield (Run 6). When oxidation of 2,4-pentanediol (30) with 1.2 molar amount of NaBrO₃/NaHSO₄, hydroxy ketone 31 was formed in 91% yield (Run 7).

Table 2. Oxidation of Various Diols by NaBrO₃/NaHSO₄<sup>a</sup>)

<table>
<thead>
<tr>
<th>Run</th>
<th>Substrate</th>
<th>Product (yield/%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>19</td>
<td>20(&lt;&lt;1)</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;)</td>
<td>23</td>
<td>24(&lt;&lt;1)</td>
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<tr>
<td>4&lt;sup&gt;d,e&lt;/sup&gt;)</td>
<td>23</td>
<td>24(&lt;&lt;1)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>) To a solution of diol (5 mmol) and NaBrO₃ (6 mmol) in CH₃CN/H₂O (10/3 mL) was added dropwise NaHSO₄ (6 mmol) in H₂O (6 mL) during a period of 15 min at room temperature under stirring for 4 h.  
<sup>b</sup>) NaBrO₃/NaHSO₄ (3.6/3.6 mol amounts).  
<sup>c</sup>) 2 h.  
<sup>d</sup>) NaBrO₃/NaHSO₄ (2.4/2.4 mol amounts).  
<sup>e</sup>) 6 h.
Oxidation of Ethers. Several methods have been developed for the direct transformation of ethers to esters. In general, although chromium and manganese reagents, such as CrO3, (PhCH2NEt2)MnO4, and Zn(MnO2)2/silica gel, are known to be good oxidants, these oxidants produce environmentally unfavorable compounds. NaBrO3 is also used in the RuO4-catalyzed oxidation of ethers. Kajigaeshi et al. showed that dibutyl- and dihexyl ethers are oxidized to the corresponding esters by NaBrO3 combined with HBr in 54 and 75% yields, respectively.7

NaBrO3/NaHSO3 reagent was found to be efficient for the oxidation of ethers to esters under mild conditions. In order to confirm the optimum reaction conditions, dioctyl ether (33) was chosen as a model substrate and allowed to react with NaBrO3/NaHSO3 under various reaction conditions (Eq. 2 and Table 3). The oxidation of 33 with 2 molar amounts of NaBrO3/NaHSO3 reagent in CH3CN/H2O produced octyl octanoate (34) and octanoic acid (35) in 67% and 27% yields, respectively (Run 1). Previously, we reported that the oxidative esterification of alcohols by the NaBrO3/NaHSO3 system was advantageously achieved in an aqueous medium.10 Hence, 33 was reacted in water to give 34 in 82% yield (Run 2). It is important that the oxidation proceeds satisfactorily in water, although the conventional oxidation by NaBrO3 in the presence of HBr is carried out in CH2Cl2. The equimolar oxidation of 33 with NaBrO3/NaHSO3 gave 34 in moderate yield, even if the reaction was prolonged to 40 h (Runs 3 and 4). Needless to say, no reaction took place when 33 was treated with NaBrO3 alone in the absence of NaHSO3 (Run 5). The same oxidation at higher temperature (60 °C) produced the α-bromo ester 36 in 32% yield together with 34 (40%) and 35 (14%) (Run 6).

We also examined the oxidation of several ethers other than 33 to verify the generality of the present procedure (Table 4). Diisopropyl ether and diundecyl ether were successfully converted into the corresponding esters in good yields (Runs 1 and 2).

It is interesting to note that the oxidation of an unsymmetrical alkyl ether with NaBrO3/NaHSO3 gave several possible esters obtained by the exchange of the alkyl group. The oxidation of ethyl octyl ether (37) produced octyl octanoate (34) (44%) rather than the expected esters, methyl nonanoate (38) (13%) and ethyl octanoate (39) (7%) (Run 3). The formation of 34 in this reaction will be discussed later. Cyclic ethers led to the corresponding lactones in good yields (Runs 4—6). For example, tetrahydrofuran led to γ-butyrolac-

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Run & Substrate & Product (yield / \%)
\hline
1 & \((\text{C}_4\text{H}_{13})_2\text{O}\) & \((\text{C}_8\text{H}_{17})\text{CO}_2\text{C}_8\text{H}_{13}\) (82) \\
 & & \((\text{CH}_3\text{H}_2\text{COOH}\) (18) \\
2 & \((\text{C}_10\text{H}_{21})_2\text{O}\) & \((\text{C}_8\text{H}_{17})\text{CO}_2\text{C}_8\text{H}_{13}\) (78) \\
 & & \((\text{CH}_3\text{H}_2\text{COOH}\) (18) \\
3 & \((\text{C}_8\text{H}_{17})\text{O}_2\text{C}_2\text{H}_5\) & \((\text{C}_8\text{H}_{17})\text{CO}_2\text{CH}_3\) (38) (13) \\
 & & \((\text{CH}_3\text{H}_2\text{CO}_2\text{C}_2\text{H}_5\) (39) (7) \\
4 & & \\
5 & & \\
6 & & \\
\hline
\end{tabular}
\caption{Oxidation of Ethers by NaBrO3/NaHSO3\textsuperscript{a)}
\end{table}

\textsuperscript{a)} Substrate (2.5 mmol) was allowed to react with NaBrO3/NaHSO3 (5/5 mmol) in H2O (10 mL) at room temperature for 16 h.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Run & \multicolumn{2}{c|}{NaBrO3} & \multicolumn{2}{c|}{NaHSO3} & \multicolumn{2}{c|}{Solvent} & Conv. & Yield (%) \\
& (mol. amounts) & (mol. amounts) & & & \% & & & \\
\hline
1 & 2 & 2 & CH3CN/H2O (5/5) & 100 & 67 & 27 & <1
2 & 2 & 2 & H2O (10) & 100 & 82 & 18 & <1
3 & 1 & 1 & H2O (10) & 62 & 34 & 4 & <1
4 & 1 & 1 & H2O (10) & 65 & 38 & 5 & <1
5 & 1 & 0 & H2O (10) & 0 & 0 & 0 & 0
6 & 2 & 2 & H2O (10) & 100 & 40 & 14 & 32
\hline
\end{tabular}
\caption{Oxidation of Dioctyl Ether (33) by NaBrO3/NaHSO3 Under Various Reaction Conditions\textsuperscript{a)}
\end{table}

\textsuperscript{a)} 33 (2.5 mmol) was allowed to react with NaBrO3/NaHSO3 at room temperature for 16 h.

b) 40 h. c) 60 °C.
tone as the sole product (Run 4). 1,3-Dihydroisobenzofuran underwent the smooth oxidation with 1.2 molar amount of NaBrO₃/NaHSO₃ affording phthalide in excellent yield (Run 5), and isochroman gave 3,4-dihydroisocoumarin in 80% yield (Run 6).

**Discussions**

During the oxidation of 1,3-cyclohexanediol 19 with 3.6 molar amounts of NaBrO₃/NaHSO₃, 2-bromo-1,3-cyclohexanedione 22 was obtained in preference to the expected 1,3-cyclohexanedione (40) (Table 2, Run 2). A plausible reaction path for the production of 22 from 19 is shown in Scheme 1. In a previous paper, we showed that enones upon treatment with NaBrO₃/NaHSO₃ are smoothly converted into the corresponding bromohydrins. Indeed, an independent reaction of 21 with NaBrO₃/NaHSO₃ (3.6 molar amounts) under the same conditions as the oxidation of 19 gave 22 in 87% yield. It is reasonable to propose that the resulting hydroxy ketone 20 was easily subjected to dehydrogenation to enone 21 in preference to dehydrogenation to 40, and the resulting 21 was bromohydrinylated to 41 and finally dehydrogenated to the 22. An alternative path for the formation of 22 via the bromination of dione 40 may be possible. Indeed, the treatment of 40 with 2.4 molar amounts of NaBrO₃/NaHSO₃ afforded 22 in 92% yield, but the fact that 40 was not detected during any stage in the oxidation of 19 with NaBrO₃/NaHSO₃ may exclude the direct bromination of 40.

As shown in Table 3, the oxidation of dioctyl ether (33) with NaBrO₃/NaHSO₃ reagent at room temperature produced the octyl octanoate 34 in good yield, while the reaction at 60 °C resulted in the α-bromo ester 36 together with 34 and octanoic acid 35. Although 36 was considered to be formed from 34, an independent reaction of 34 with 2 molar amounts of NaBrO₃/NaHSO₃ reagent at 60 °C produced a small amount of 35, but not bromo ester 36.

In a previous paper, we showed that the reaction of cyclohexene with NaBrO₃/NaHSO₃ proceeds via the bromonium ion mechanism to produce trans-2-bromocyclohexan-1-ol in high selectivity, but no product, such as 1-bromo-2-cyclohexene, which is considered to be formed via radical process, is produced. In view of these facts and results obtained here, the oxidation of ethers with NaBrO₃/NaHSO₃ reagent seems to involve an ionic process rather than a radical process. Thus, a plausible reaction path for the oxidation of 33 with NaBrO₃/NaHSO₃ reagent is shown in Scheme 2. The reaction is thought to be initiated by the abstraction of hydride ion from 33 by NaBrO₃/NaHSO₃ to form an oxonium ion A which appears to be immediately converted into a hemiacetal B, followed by ester 34 via the oxidative dehydrogenation of B. At higher temperature, the dehydration of acetal B to alkynol ether C may be possible. Under these conditions, C is believed to be subject to bromohydroxylation with NaBrO₃/NaHSO₃ to form bromohydrin E, which is subsequently oxidized to the α-bromo ester 36. Indeed, the treatment of ethyl 1-heptenyl ether (42) by NaBrO₃/NaHSO₃ (2 molar amounts) at 60 °C for 16 h afforded ethyl 2-bromoheptanoate (43) (12%), 2-bromohexanoic acid (44) (35%) and hydrated products, 45 (11%) and 46 (22%) (Eq. 3).

![Scheme 1](image1.png)

Scheme 1. A Possible Reaction Path for the Oxidation of 1,3-Cyclohexanediol (19) by NaBrO₃/NaHSO₃.

![Scheme 2](image2.png)

Scheme 2. A Possible Reaction Path for the Oxidation of Diocyl Ether (33) by NaBrO₃/NaHSO₃.

In the oxidation of unsymmetrical ethyl octyl ether 37, we showed that the unexpected product, octyl octanoate 34, was formed in 44% yield along with the expected esters, 38 (13%) and 39 (7%) (Table 4, Run 3). In order to obtain information on the formation of 34 by the exchange reaction between 38 and 39, an equimolar mixture of 38 and 39 was allowed to react with NaBrO₃/NaHSO₃ under the same conditions as the oxidation of 37. However, ester 34 was not obtained.
Hence, it is reasonable to predict that 34 is not formed by transesterification between 38 and 39. We would like to suggest the following reaction path for the oxidation of 37 with NaBrO₃/NaHSO₃ (Scheme 3). At the early stage of the reaction, hemiacetals F and G are probably formed, and are in equilibrium with the corresponding aldehydes and alcohols. The exchange reactions among the hemiacetals would result in four possible hemiacetals, (F, G, H, and I) (Scheme 4). The heat of formation of these hemiacetals calculated using the PM3 method showed that H is the most stable product. Consequently, the formation of 34 is preferred over the other esters. This observation is in accord with the experimental result for the oxidation of 37.

In conclusion, the oxidation of diols and ethers was successfully achieved by using NaBrO₃/NaHSO₃ reagent under mild conditions. This provides a convenient methodology for the selective oxidation of diols and ethers in high yields.

Experimental

General Procedures. Diols and ethers except for 17 and 37 were commercially available. Compounds 17 and 37 were synthesized by conventional methods. GC analysis was performed with a flame ionization detector using a 0.2 mm × 25 m capillary column (OV-1, OV-17). ¹H- and ¹³C NMR were measured at 270 and 67.5 MHz, respectively, in CDCl₃ with Me₄Si as the internal standard. Infrared (IR) spectra were measured using NaCl plates or KBr disks. GC-MS spectra were obtained at an ionization energy of 70 eV. The yields of the products were estimated from the peak areas based on the internal-standard technique.

General Procedures for the Oxidation of Diols with NaBrO₃/NaHSO₃ Reagent. To a solution of NaBrO₃ (12 mmol) in water (6 mL) was added the diols (5 mmol) in acetonitrile (10 mL) followed by the dropwise addition of a solution of NaHSO₃ (12 mmol) in water (12 mL) over a period of about 15—30 min. The mixture was then stirred at room temperature for 2—6 h. The reaction mixture was poured into 50 mL of ether. After separation of the organic phase, the aqueous layer was extracted twice with ether. The combined organic layer was washed with anhydrous Na₂S₂O₅ solution and dried over MgSO₄. After filtration, the ether was removed in vacuum, and the residue was purified by column chromatography (silica gel, hexane : ethyl acetate = 10 : 1) to give the α-hydroxy ketone and/or diketone. The products were identified through a comparison of the isolated products with authentic samples.

General Procedures for the Oxidation of Ethers with NaBrO₃/NaHSO₃ Reagent. To a solution of NaBrO₃ (5 mmol) in water (5 mL) was added ether (2.5 mmol) followed by the dropwise addition of a solution of NaHSO₃ (5 mmol) in water (5 mL) over a period of about 15 min; the mixture was stirred at room temperature for 16 h. The products were purified by the same method as previously described.

The products were identified by a comparison of their spectral data with those obtained by esterification between the corresponding acids and alcohols in the presence of sulfuric acid in refluxing dichloromethane. 3,4-Dihydroisocoumarin was identified by a comparison to its previously reported spectral data.

Octyl 2-Bromoocatcanoate (36): ¹H NMR (CDCl₃/Me₄Si) δ = 4.23—4.14 (m, 3 H), 2.06—1.99 (m, 2 H), 1.69—1.61 (m, 2 H), 1.41—1.26 (m, 20 H), 0.89 (t, J = 6.74 Hz, 6H); ¹³C NMR (CDCl₃/Me₄Si) δ = 169.9, 65.9, 46.1, 34.9, 31.7, 31.4, 29.1, 28.4, 28.3, 27.5, 25.7, 22.5, 22.4, 14.0, 13.9.

Reaction of 1-Ethoxy-1-heptene (42) with NaBrO₃/NaHSO₃ Reagent. The starting material 42 was synthesized using literature procedures. To a solution of NaBrO₃ (5 mmol) in water (5 mL) was added 42 (2.5 mmol) followed by the dropwise addition of a solution of NaHSO₃ (5 mmol) in water (5 mL) over a period of about 15 min. The mixture was then stirred at 60 °C for 16 h. The products, 43 and 45, were purified by the same method as previously described. Compounds 44 and 46 were isolated as the ethyl esters, 43 and 45, respectively, after a treatment of the reaction mixture with ethanol in the presence of a catalytic amount of sulfuric acid.

Ethyl 2-Bromoheptanoate (43): ¹H NMR (CDCl₃/Me₄Si) δ = 4.27—4.11 (m, 3 H), 2.06—1.96 (m, 2 H), 1.38—1.22 (m, 6 H), 1.03 (t, J = 7.26 Hz, 3 H), 0.89 (t, J = 6.60 Hz, 3 H); ¹³C NMR (CDCl₃/Me₄Si) δ = 169.9, 61.8, 46.1, 34.8, 30.9, 26.9, 22.3, 13.9, 13.8.

We thank Japan Private University Foundation for financial support.
References


