Synthesis and Properties of 2-Oxa-6-azaspiro[3.3]heptane Sulfonate Salts

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Abstract
An improved synthesis of the bicyclic spiro compound 2-oxa-6-azaspiro[3.3]heptane is presented. While this compound is often isolated as an oxalate salt, its isolation as a sulfonic acid salt yields a more stable and more soluble product. With these improved properties access to a wider range of reaction conditions with the spirobicyclic 2-oxa-6-azaspiro[3.3]heptane has been enabled.

Key words azetidines, oxetanes, spiro compounds, hydrogenolysis, salt formation

Introduction
Recently, the increasing need for three dimensionally shaped heterocyclic ring systems resulted in a rapidly growing interest in the application of the 2-oxa-2-azaspiro[3.3]heptane fragment as a building block for new drug candidates.3,4 For instance, this moiety was reported to be a structural surrogate for morpholine in a number of drug-like molecules.3 Until recently, 2-oxa-6-azaspiro[3.3]heptane (4) was usually prepared from tribromopentaerythritol (1b) (also known as FR-513, a commercially available flame retardant) via the method first described by Carreira et al. (Scheme 1).4 This route involves a cyclization reaction under basic conditions with p-toluenesulfonyl chloride (2) towards the N-tosylated spiro compound 3, followed by removal of the tosyl group. The deprotection step is performed by sonication of a mixture of intermediate 3 and magnesium turnings in methanol at room temperature during a period of one hour. A sluggish filtration to remove the magnesium salts formed in the deprotection reaction and treatment of the filtrate with oxalic acid affords the oxalate salt 4a. The first literature example utilizing this approach describes an experiment on a five gram scale, which yielded the hemioxalate salt 4a in 81% yield.

Scheme 1 Preparation of 2-oxa-6-azaspiro[3.3]heptane oxalate salt (4a) via the method developed by Carreira et al.

However, the scalability of this process to a scale bigger than one kilogram of the oxalate 4a is challenging.3,4 Specifically the removal of magnesium salts by filtration was found to be sluggish and a lot of the product was lost at this stage. Already on a 100 g scale, the oxalate salt 4a was isolated in yields of only 47% or less. Moreover, as the literature also points out, the oxalate product may contain partially hydrated oxalic acid, which hampers an easy determination of the actual content of 2-oxa-6-azaspiro[3.3]heptane.4b At the same time, complex equipment is required for the sonication conditions used in the deprotection step.

A patent application5 describes a variation of a 100 g scale experiment in which the use of sonication in the deprotection step is replaced by refluxing in methanol. The magnesium is then added in portions, to avoid a too strong exothermic effect and after completion of the reaction the magnesium salts are removed in a similar manner as described above. Additionally, the application describes investigations towards alternative acids for the salt formation step including hydrochloric acid, p-toluenesulfonic acid, and acetic acid (Scheme 2).
According to this patent application, both HCl and p-toluenesulfonic acid proved to be unsuccessful. In the case of p-toluenesulfonic acid, a viscous undefined material was obtained while HCl resulted in ring opening of the oxetane moiety. However, using acetic acid, 2-oxa-6-azaspiro[3.3]heptane acetate (4b) was isolated in 86% yield on a 100 g scale, by simply evaporating a solution of the amine in methanol and acetic acid. Compared with the oxalate (yield 67%) a slightly better product yield was obtained, but a major advantage of the acetate salt was that the composition of the isolated material could now be determined via ¹H NMR spectroscopy. In addition, it is much easier to remove an excess of acetic acid by (co-)evaporation.

In a recent paper, the authors describe that in an attempt to scale up the original procedure for the preparation of oxalate 4a, the reductive removal of the tosyl protecting group from intermediate 3 at 100 L scale turned out to be even more problematic. Though conversion was good, much material was lost during the workup, and low yields (<35%) of poor quality material were observed. For this reason, the authors switched to a benzyl-protecting group, leading to a more operable deprotection and workup procedure (Scheme 3). Ultimately, this approach was proven on scale, and a total of 65 kg of the oxalate salt 4a was prepared in two batches. Interestingly, this route involves precipitation of the crude benzyl protected 2-oxa-6-azaspiro[3.3]heptane with HCl yielding the bench-stable HCl salt 6c. Also in our hands, this approach was proven to work well and no significant oxetane ring opening reaction was observed during the precipitation step. The authors did not comment in detail on the moderate yield in compound 6c, but it is likely that concurrent formation of undesired 3,3-bis(benzylaminomethyl)oxetane (7) as side product is the major cause (Scheme 4).

In a recent project, driven by a demand for large quantities of 2-oxa-6-azaspiro[3.3]heptane (4), we initially prepared the compound on a multi-kilogram scale utilizing the reductive removal of the tosyl protective group in compound 3. In line with the reported observations, we also struggled with a tedious workup procedure. Thus, to improve the protocol, we decided to explore alternative protecting groups involved in the preparation of compound 4 anticipating a high impact. In addition, the follow-up chemistry revealed challenges related to thermal decomposition and a poor solubility of the oxalate 4a. Moreover, it was difficult to follow the reaction progress and the reaction could only be performed in a limited concentration range. For these reasons, the evaluation of different non-oxalate salts became a topic of interest.

In this article, we describe a new scalable and reliable synthetic procedure for the preparation of spiro compound 4 utilizing sulfonate salts. Also the stability of the isolated sulfonate salts in methanol and their application has been investigated in a model reaction.

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In this article, we describe a new scalable and reliable synthetic procedure for the preparation of spiro compound 4 utilizing sulfonate salts. Also the stability of the isolated sulfonate salts in methanol and their application has been investigated in a model reaction.
Results and Discussion

As depicted in the general route (Scheme 5), it is possible to prepare the N-protected 2-oxa-6-azaspiro[3.3]heptane 8 in either one or two steps, and both approaches were investigated. Initially, we investigated 16 different protecting groups using corresponding amines in cyclization reactions towards N-protected 2-oxa-6-azaspiro[3.3]heptanes (Figure 1). After a series of test experiments, five amines, including tosyl-, o-nosyl-, p-nosyl-, benzyl-, and 4-methoxybenzylamine, were found suitable for this application (Table 1).

![Scheme 5: Two possible approaches towards 2-oxa-6-azaspiro[3.3]heptane and its acid salts](image)

![Figure 1: List of amines initially investigated for the cyclization reaction towards 2-oxa-6-azaspiro[3.3]heptane derivatives](image)

The tosyl-protected analogue could be directly prepared from erythritol tribromide according to the literature procedure.4b Table 1 summarizes the results obtained from the amines that were participating in the envisioned cyclization when stirred with DBU in DMF at 80 °C. The analogues with o-nosyl- (XVI), p-nosyl- (XV), benzyl (I), and 4-methoxybenzyl (III) as N-protecting group were successfully prepared on gram scale by cyclization with 3,3-bis(halogenmethyl)oxetane 5a or 5b in DMF at 80 °C using DBU as base. For most of the other amines the preparation of N-protected 2-oxa-6-azaspiro[3.3]heptanes either failed or was not investigated because of safety issues or incompatible deprotection conditions.

![Table 1: Preparation of N-Protected 2-Oxa-6-azaspiro[3.3]Heptane Derivatives](image)

It was found that both 3,3-bis(chloromethyl)oxetane (5a) and its bromo analogue 5b are suitable for these syntheses, but overall, reactions were much faster with 3,3-bis(bromomethyl)oxetane (5b). The crude oxetane 5b is generally obtained in good purity (>90%) but when necessary it may also be purified by distillation (56 °C/0.10 mbar).

In the next step, we focused on the preparation of the benzyl derivative 6, as we expected its deprotection to be more promising than utilizing sulfonamides using a simple palladium-catalyzed hydrogenolysis with formation of tolueno as a volatile by-product. First, the synthesis of N-benzyl-2-oxa-6-azaspiro[3.3]heptane (6) was screened in order to investigate the effect of solvents (1,4-dioxane, MeCN, and DMF), substrate concentration (100 or 50 mg/mL), and base (DIPEA, K2CO3, Cs2CO3, DBU, and K3PO4) on the conversion...
Preparation of the PTSA salt was also tested in n-butanol as a less polar solvent and indeed, a precipitate was formed almost immediately after adding the acid and after 1.5 hours, the expected salt was collected by filtration in 67% yield with good purity. The salt formation with PTSA was further investigated using a slightly modified procedure. Additionally, the salt formation was also investigated with nine other acids (Scheme 6, Table 3).

Among the mono acids only the two sulfonate salts 4d and 4k could directly be filtered off from the reaction mixture and both gave an easy to handle solid in good yield. The benzoate salt 4f did not precipitate and after trituration a very hygroscopic material was obtained. No solid could be isolated from the experiment with mandelic acid. Notably, at 25 °C the PTSA salt 4d remained in solution, but upon cooling down also this experiment gave the expected salt in good yield. This time no ring opening product was observed, probably due to the use of equimolar amounts of acid.

Except for malic acid all bivalent acids resulted in precipitation of the expected salts from the reaction mixture. The benchmark experiment with 0.50 equivalent of oxalic acid gave the hemioxalate salt 4s in 85% yield while with 1,5-napthalenedisulfonic acid (Armstrong’s acid) the salt 4r was isolated as a fine crystalline powder in an excellent 94% yield. All other hemic acids were obtained in poor yields and the isolated salts from sulfuric (4m), fumaric (4n), and

<table>
<thead>
<tr>
<th>Salt</th>
<th>Acid</th>
<th>Yield (%)</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>oxalic</td>
<td>54</td>
<td>white powder</td>
</tr>
<tr>
<td>4c</td>
<td>HClb</td>
<td>23c</td>
<td>sticky solid</td>
</tr>
<tr>
<td>4d</td>
<td>PTSA</td>
<td>65c</td>
<td>white powderd</td>
</tr>
<tr>
<td></td>
<td>PTSA (n-BuOH)</td>
<td>67</td>
<td>white powder</td>
</tr>
<tr>
<td>4e</td>
<td>TFA</td>
<td>56e</td>
<td>sticky solid</td>
</tr>
<tr>
<td>4f</td>
<td>citric acid</td>
<td>–</td>
<td>viscous oil</td>
</tr>
<tr>
<td>4g</td>
<td>MeSO₃H</td>
<td>–</td>
<td>viscous oild</td>
</tr>
<tr>
<td>4h</td>
<td>camphor sulfonic acid</td>
<td>55</td>
<td>white powder</td>
</tr>
</tbody>
</table>

a Conditions: To a stirred solution of 2-oxa-6-azaspiro[3.3]heptane acetate (4b, 100 mg) in MeOH (1.0 mL) at r.t. was added 1.1 equivalent of the acid. The resulting mixture was stirred at r.t. for 1.5 h after which precipitates were filtered off. When no precipitate was formed, the solvent was removed and the residue was triturated with Et₂O (2.0 mL).

b A solution of 3 N HCl in MeOH was used.

c These salts were obtained after concentration and trituration with Et₂O.

d Contains impurities.
tartaric acid (4q) were slightly hygroscopic. After removal of the solvent, the malic acid salt 4p could be isolated as a dry powder via trituration in MTBE.

In conclusion, the 2-oxa-6-azaspiro[3.3]heptane could easily be isolated as a salt with a number of acids and on small scale, especially the hemi-1,5-naphthalenedisulfonic acid salt 4r, the PTSA salt (4d, 97% yield), and hemioxalate salt (4s, 86% yield) were obtained in excellent yields.

**Scale-Up**

Next, the preparation of 2-oxa-6-azaspiro[3.3]heptane hemi-naphthalene-1,5-disulfonate salt 4r was scaled up starting from 200 g of tribromopentaerythritol (Scheme 7). After distillation of the 3,3-bis(bromomethyl)oxetane, the subsequent ring closure with benzylation followed by distillation yielded N benzyl-2-oxa-6-azaspiro[3.3]heptane (6) in good yield (60% in 2 steps) and purity. The hydrogenolysis of N benzyl-2-oxa-6-azaspiro[3.3]heptane (6) was successful on that scale under the conditions described above. After filtration and partial concentration, treatment with 0.50 equivalent of naphthalene-1,5-disulfonic acid yielded the desired 2-oxa-6-azaspiro[3.3]heptane as its hemisulfonate salt in 84% yield with a purity assay of 96%. Overall the 2-oxa-6-azaspiro[3.3]heptane salt 4r could be prepared in three steps from tribromopentaerythritol with an unprecedented overall yield of 50%.

**Stability Studies**

It was mentioned in literature that differential scanning calorimetry (DSC) analysis of the oxalate salt as well as the free base indicated that both compounds exhibit a relatively low thermostability with significant heat release (>1000 J/g).2 This means that safe working conditions on large scale should be ensured and for this reason we also investigated the stability of the isolated sulfonate salts 4d and 4r.

As described above, it was shown that the sulfonate salts can be isolated as bench stable compounds. However, since it was also observed that ring opening of the oxetane ring occurs with an excess of sulfonic acid the amount of acid should be carefully dosed when preparing these salts. The question arose if the salt 4d itself is stable and this was tested on 100 mg scale by stirring it overnight in a methanolic solution at reflux temperature. But still the pure and crystalline PTSA salt 4d could be recovered in 83% yield after trituration with MTBE.

The thermal stability of the isolated sulfonate salts 4d and 4r was further investigated by DSC analysis and compared with both the oxalate and the hemioxalate salts 4a and 4s, respectively. As shown in Figure 2, both sulfonate salts were stable at temperatures up to 176 °C (4d) and 200 °C (4r). Contrary, the oxalate salts appear to decompose at much lower temperatures of 145 °C (4a) and 143 °C (hemi salt 4s) with broad decomposition temperature ranges. Even the free base was found to be rather unstable (peak at 156 °C, onset around 110 °C). Similar observations were made using the melting apparatus. While the tosylate salt initially showed a clear melting point around 182 °C other compounds were found to decompose around the peak temperatures observed in the DSC analyses. These stability

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**Table 3** Formation of Salts from 4b at 0 °C on a 200 mg Scale4

<table>
<thead>
<tr>
<th>Salt</th>
<th>Acid (equiv)</th>
<th>Precipitation at 0 °C</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4d</td>
<td>PTSA (1.0)</td>
<td>yes</td>
<td>97</td>
</tr>
<tr>
<td>4d</td>
<td>PTSA (1.0)b</td>
<td>no³</td>
<td>85</td>
</tr>
<tr>
<td>4i</td>
<td>M-mandelic (1.0)</td>
<td>no</td>
<td>0</td>
</tr>
<tr>
<td>4j³</td>
<td>benzoic (1.0)</td>
<td>no⁰</td>
<td>64</td>
</tr>
<tr>
<td>4k</td>
<td>2-naphthalenesulfonic acid (1.0)</td>
<td>yes</td>
<td>76</td>
</tr>
<tr>
<td>4m⁷</td>
<td>H₂SO₄ (0.5)</td>
<td>yes</td>
<td>56⁵</td>
</tr>
<tr>
<td>4n⁶</td>
<td>fumaric acid (0.5)</td>
<td>yes</td>
<td>51¹</td>
</tr>
<tr>
<td>4p</td>
<td>malic acid (0.5)</td>
<td>no³</td>
<td>61¹</td>
</tr>
<tr>
<td>4q³</td>
<td>ß-tartaric acid (0.5)</td>
<td>yes</td>
<td>7¹</td>
</tr>
<tr>
<td>4r</td>
<td>1,5-naphthalenesulfonic acid (0.5)</td>
<td>yes</td>
<td>94¹</td>
</tr>
<tr>
<td>4s</td>
<td>oxalic acid (0.5)</td>
<td>yes</td>
<td>86¹</td>
</tr>
</tbody>
</table>

4 Conditions: To a stirred solution of 2-oxa-6-azaspiro[3.3]heptane acetate (4b, 200 mg) in MeOH (2 mL) at 0 °C was added 1 equiv of monoaic or 0.5 equiv of diacid as a solution in EtOH (2 mL). The resulting mixture was stirred at 0 °C for 1 h after which the precipitate was collected by filtration.

b Salt formation tested at r.t.

³ Isolated as hygroscopic salts.

¹ When no precipitate was formed, the mixture was concentrated and the residue was triturated with MTBE (3 mL).

f Assumed to be the hemi salt.
observations led to the conclusion that the better solubility of the sulfonate salts combined with their better stability should open new perspectives for synthetic applications of 2-oxa-6-azaspiro[3.3]heptane.

Application in Synthesis

While the oxalate salts are barely soluble in most solvents, it is to be expected that the sulfonate salts have a wider solvent window for chemical conversions. In the literature, most reactions performed with both oxalate salts are usually performed in either highly polar solvents such as DMSO or DMF or in a refluxing less polar solvent. The latter solvents often give rise to poor isolated product yields. We tested the aromatic nucleophilic substitution reaction of 2-oxa-6-azaspiro[3.3]heptane sulfonate salts 4d and 4r and hemioxalate salt 4s (1.0 equiv) with 2-chloropyrimidine (10) in acetonitrile using diisopropylethylamine (2 equiv) as base (Scheme 8). Within 30 minutes at 40 °C the two sulfonate salts indeed showed partial conversion in acetonitrile while the hemioxalate salt showed no reaction at all (Table 4). Notably, under these conditions the reaction mixture with tosylate salt 4d gave a clear solution. After stirring for 66 hours at room temperature, sulfonate salt 4r showed full conversion in a clean reaction. The tosylate salt 4d stalled at 88% conversion. Aqueous workup of the reaction with PTSA salt 4r yielded 71% of the expected adduct 11. In contrast, the oxalate 4s still showed only 10% conversion after 66 hours at 40 °C. Similar results were obtained when testing the reactions in THF. However, due to a lower solubility of the three salts in this solvent the reaction slowed down significantly and while the sulfonate salts gave partial conversion, the oxalate gave no reaction at all. Notably, even in MTBE good conversion was observed with PTSA salt 4r. These results confirm that most likely the better reactivity of the sulfonate salts should be ascribed to their better solubility in most solvents.

![Figure 2](image-url)  
**Figure 2** DSC analyses of 2-oxa-6-azaspiro[3.3]heptane (4) and its salts: oxalate 4a, hemioxalate 4s, p-toluenesulfonate 4d, and hemi-naphthalenedisulfonate 4r.
Conclusion

In summary, a robust and scalable preparation of the bicyclic spiro compound 2-oxa-6-azaspiro[3.3]heptane sulfonate salts has been presented. In a model reaction, these sulfonate salts were shown to allow for a wider range of reaction conditions compared to the commercially available oxalate salt 4s and among the tested salts PTSA salt 4d shows the highest reaction rate.

All solvents and reagents were obtained from commercial sources and were used without purification. Products and intermediates were purified by distillation or by crystallization. Reactions were conducted under a N₂ atmosphere, unless stated otherwise. ¹H NMR spectra were recorded in CDCl₃, DMSO-d₆, or D₂O using a Bruker Biospin NMR apparatus at 400 MHz; chemical shifts (δ) are reported versus TMS as an internal standard. GC/MS chromatograms were measured using an Agilent system (1100 Binary Pump, G1312A, degasser; autosampler, CoLCom, DAD detector: Agilent G1315B, 220–320 nm, MSD: Agilent LC/MSD G6130B ESI, LCMS chromatograms were measured using an Agilent system (1100 Binary Pump, G1312A, degasser; autosampler, CoLCom, DAD detector: Agilent G1315B, 220–320 nm, MSD: Agilent LC/MSD G6130B ESI, pos/neg 100–800). Melting points were determined with a Büchi.

3.3-Bis(bromomethyl)oxetane (5b)
An oven-dried reaction flask was charged with pentaerythritol tribromide (200 g, 616 mmol) and absolute EtOH (1 L). At temperature <20 °C, a freshly prepared NaOEt (253 mL, 677 mmol, 21% in methanol (~256 mmol/L). The reaction mixture was heated to reflux (76 °C) and a suspension was formed. After 3 h, GC analysis showed full conversion of the pentaerythritol. The reaction mixture was cooled to r.t. and the solid material was removed by filtration. The filtrate was partitioned between MTBE (400 mL) and H₂O (550 mL). The aqueous phase was extracted with MTBE (250 mL). The combined organic phases were washed successively with H₂O (250 mL) and brine (250 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was distilled with a short path distillation setup (62 °C/0.10 mbar) and 130 g (85%) of 5b was collected as a colorless oil.

3.3-Bis(chloromethyl)oxetane (5a)
Prepared according to the literature procedure. Product was isolated as a colorless oil after bulb-to-bulb distillation (62 °C/0.10 mbar).

6-Benzyl-2-oxa-6-azaspiro[3.3]heptane (6)
In a 2 L reaction flask, bis(bromomethyl)oxetane (5b; 129 g, 518 mmol) was dissolved in anhyd DMF (1300 mL). At r.t., benzylamine (113.6 g, 745 mmol) and DBU (59.5, 391 mmol) was added, followed by AcOH (2.15 g, 35.9 mmol). The autoclave was closed and flushed three times with H₂ (4 bar). The stirrer was started and 5 bar of H₂ pressure was applied. The reaction mixture was hydrolyzed by stirring for 30 min at 30 °C for 24 h. The mixture was cooled and filtered through Celite. The filtrate was concentrated in vacuo to a volume of ~1400 mL, which yielded a concentrated solution of free base in methanol (~256 mL/L).
Using the same protocol, the same salt 4r was also prepared starting from 6-(4-methoxybenzyl)-2-oxa-6-azaspiro[3.3]heptane (9) on a 5.00 g scale giving 4.10 g of the desired product (74%).

2-Oxa-6-azaspiro[3.3]heptane Acetate (4b)
A 500 mL glass autoclave was charged with 6-benzyl-2-oxa-6-azaspiro[3.3]heptane (6; 8.00 g, 42.3 mmol) and MeOH (160 mL). The autoclave was flushed with N₂ and Pd/C (10% w/w, nonreduced, Acros, 4.50 g, 4.23 mmol) was added, followed by AcOH (2.56 g, 42.7 mmol). The autoclave was closed and flushed three times with H₂ (3 bar) before the final pressure of 5 bar was applied. The reaction was allowed to stir for 18 h at 30 °C. The autoclave was flushed with N₂ (3 bar) before the final pressure of 5 bar was applied. The reaction was complete when the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (4 mL) and sat. aq Na₂CO₃ (4 mL). The organic phase was separated, dried (Na₂SO₄), and concentrated under reduced pressure to yield 110 mg (71%) of a white powder; mp 109–110 °C.

1H NMR (DMSO-d₆, 400 MHz): δ = 8.32 (d, J = 4.8 Hz, 2 H), 6.57 (t, J = 4.8 Hz, 1 H), 4.87 (s, 4 H), 4.30 (s, 4 H).

13C NMR (DMSO-d₆, 100 MHz): δ = 162.5 (C), 157.8 (CH), 110.6 (CH), 79.9 (CH₂), 59.2 (CH₂), 38.1 (C).

2-Oxa-6-azaspiro[3.3]heptane p-toluenesulfonate (4d)
A 100 mL glass autoclave was charged with 6-benzyl-2-oxa-6-azaspiro[3.3]heptane (6; 2.00 g, 10.6 mmol) and MeOH (40 mL). The autoclave was flushed with N₂ and Pd/C (10% w/w, nonreduced, Acros, 1.12 g, 1.06 mmol) was added, followed by AcOH (698 mg, 11.6 mmol). The autoclave was closed and flushed three times with H₂O (4 bar) before the final pressure of 5 bar was applied. The reaction was allowed to stir for 18 h at 30 °C. The autoclave was flushed with N₂ (3 bar) before the final pressure of 5 bar was applied. The reaction was complete when the mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc (4 mL) and sat. aq Na₂CO₃ (4 mL). The organic phase was separated, dried (Na₂SO₄), and concentrated under reduced pressure to yield 110 mg (71%) of a white powder; mp 109–110 °C.

1H NMR (DMSO-d₆, 400 MHz): δ = 8.0–7.0 (s, 2 H + H₂O from solvent), 4.61 (s, 4 H), 3.85 (s, 4 H), 1.78 (s, 3 H).

References
(6) (a) Miller, D.; Clark, P.; Melton, T. British Patent GB1169027, 1966. (b) So far, only the preparation of the p-toluenesulfonate salt 6d from freshly distilled free base 6 has been described, however, the yield was only 26%.
(7) The purity assay was determined by quantitative 1H NMR spectroscopy with pentaerythritol as internal standard.