Synthesis of Bicyclo[3.1.0]hexan-2-ones by Manganese(III) Oxidation in Ethanol

Kentaro Asahi,* Hiroshi Nishino

Abstract: N-Propenyl-3-oxobutanamides underwent the manganese(III)-induced oxidative intramolecular cyclization in ethanol to produce 3-aza-bicyclo[3.1.0]hexan-2-ones in good yields. A similar reaction of propenyl 3-oxobutanamides and S-propenyl 3-oxobutanethioates also gave the corresponding 3-oxa- and 3-thiabicyclo[3.1.0]hexan-2-ones. The reaction details, the structure determination, and the reaction pathway are described.

Key words: cyclizations, oxidations, radical reactions, bicyclo[3.1.0]hexanones, manganese(III) acetate

The 3-aza- and 3-oxabicyclo[3.1.0]hexanes and their derivatives consisting of a flat and very rigid cyclopropane-fused γ-lactam or γ-lactone ring are found in a number of biologically and pharmacologically active compounds.1 For example, the commercially available procymidone is a gray mold disease inhibitor,1b and marasmic acid isolated from Marasmius conigenus displays a significant antimicrobial activity.1d,2 Therefore, several research groups have investigated the synthesis of the 3-aza- and 3-oxabicyclo[3.1.0]hexanes, and many useful methods have been reported.3 The aza- and oxabicyclo[3.1.0]hexanes can also be easily converted into useful synthetic intermediates, such as the cis-1,2-cyclopropylamino acids and conformationally restricted cis-1,2-bis(hydroxymethyl)cyclopropanes.1c

In recent years, we have developed the manganese(III) acetate mediated radical cyclization reaction using simple olefins and 1,3-dicarboxyl compounds, which have been effective for the synthesis of highly functionalized heterocyclic compounds.4 The characteristics of the reaction is that the facile ligand exchange of the manganese(III) acetate with 1,3-dicarbonyl compounds to generate the manganese(III)-enolate complex in situ, followed by the one-electron transfer from an electron-rich C=C bond to the complex, produces the corresponding carbon radicals.4,5 The radicals have been utilized for the carbon–carbon bond formation in both an inter- and intramolecular fashion to yield various cyclic compounds.4,6 In connection with these studies, Bertrand,7a,b Orena,7c and Brown7d–f reported the synthesis of the 3-aza-, and 3-oxabicyclo[3.1.0]hexan-2-ones with no substituent at the C-6 position using the manganese(III)–copper(II) oxidation system. Although many pharmacologically active bicyclo[3.1.0]hexan-2-ones4 have no substituent at the C-6 position, it is important to examine the synthesis of the C-6 functionalized analogues using the manganese(III) oxidation system since the substituent effect of the olefin is essential for the manganese(III) oxidation sequence.6 Moreover, there have been few reports on the synthesis of 3-thiabicyclo[3.1.0]hexanes8 even if the compounds showed antibacterial activities.1g,h Therefore, we investigated the synthesis of the 3-aza-, 3-oxa-, and 3-thiabicyclo[3.1.0]hexan-2-ones using N-propenyl-3-oxobutanamides, propenyl 3-oxobutanamides, and S-propenyl 3-oxobutanethioates in order to develop the synthesis of functionalized cyclopropane-fused γ-lactams, γ-lactones and γ-thiolactones.9a,b,c,d In this paper, we wish to report the successful results of their synthesis in ethanol as the solvent that has been only less used in the manganese(III)-based oxidation, and also discuss the limitation of the reaction from the standpoint of the substituents in the olefin.

First of all, the reaction of N-propenyl-N-benzyl-3-oxobutanamide 1a (0.5 mmol) with manganese(III) acetate dihydrate (1.5 mmol) was carried out in glacial acetic acid (20 mL) at reflux temperature under argon. The butanamide 1a was consumed within 30 seconds and underwent oxidative intramolecular cyclization to produce the 3-aza-bicyclo[3.1.0]hexan-2-one 2a (48%) (entry 1). A comparable result was also obtained in the case of the N-methyl-substituted 3-oxobutanamide 1b (entry 4). The reaction at 85 °C improved the yield of 2a together with 3a (entry 2). Since the azabicyclo[3.1.0]hexanone 2a and the pyrrolidinone 3a might be formed from the same intermediate, the pyrrolidinone 3a was heated under reflux in acetic acid for conversion into 2a.4c-d However, the reaction caused only the decomposition of 3a. It is known that the mild manganese(III)-based oxidation was carried out in ethanol as the solvent,9 which was sometimes effective for the cyclization.6 Therefore, we changed the solvent from acetic acid to ethanol and examined the reaction. Fortunately, the desired azabicyclo[3.1.0]hexanone 2a was obtained as the sole product (88%) (entry 3).

The structure of 2a was determined on the basis of the 1H NMR, 13C NMR, and IR spectra as well as the combustion

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Table 1 Oxidation of N-Propenyl-3-oxobutanamides 1a–q with Manganese(III) Acetate Dihydrate

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* The reaction of N-propenyl-3-oxobutanamide (0.5 mmol) was carried out in EtOH or glacial AcOH (20 mL) in the presence of Mn(OAc)3·2H2O. Before the reaction, the mixture was degassed under reduced pressure for 30 min using an ultrasonicator followed by argon displacement.
* Molar ratio.
* Isolated yield based on the amount of the N-propenyl-3-oxobutanamide used.
* The butanamide 1i was recovered in 29%.
* The butanamide 1j was recovered in 27%.
* Cu(OAc)2 (0.60 mmol) was also added as a co-oxidant.
* The product 2o was obtained as a 17:6 diastereoisomeric mixture.
* The butanamide 1p was recovered in 14%.
analysis and high-resolution mass spectrum. The $^1$H NMR spectrum of 2a showed a doublet of doublet at $\delta = 3.43$ (1 H, $J = 11.0, 6.4$ Hz) and a broad doublet at $\delta = 2.99$ (1 H, $J = 11.0$ Hz) assigned to the H-4 methylene protons, and a broad doublet at $\delta = 3.33$ (1 H, $J = 6.4$ Hz) due to the H-5 methine proton, which was deshielded by the anisotropic effect of one of the phenyl groups substituted at C-6. It is suggested that the dihedral angle between one of the H-4 protons and H-5 proton must be ca. 90° based on the observed coupling constant. In the $^{13}$C NMR spectrum, two quaternary carbons and a tertiary carbon appeared at $\delta = 52.5$ (C-1), 50.6 (C-6), and 26.7 (C-5), respectively, assigned to the characteristic peaks of the cyclopropane ring. All the peaks in the NMR spectrum were also correlated by the H-H COSY and H-C COSY. In addition, the keto and amide carbonyls appeared at 1697 and 1682 cm$^{-1}$ in the IR spectrum and $\delta = 200.4$ and 168.8 in the $^{13}$C NMR spectrum. These spectroscopic data agreed with the structure.

A similar reaction of other N-propenyl-3-oxobutanamides 1b–h also gave successful results (entries 5–11). The reaction of 1i and 1j was not effective because of the steric hindrance of the N-protecting phenyl group in 1i and the sensitivity of the secondary amide group in 1j to the oxidant (entries 12 and 13). The bis(4-methylphenyl)-substituted butanamide 1k predominantly produced the pyrrolidinones 3k and 4k (entry 14). The electron-donating ability of the 4-methylphenyl group probably resulted in the oxidation of the tertiary radical prior to the cyclization. The alkenes 1l–n bearing the electron-withdrawing group on the R$^1$ and R$^2$ aryl groups also afforded the azabicyclo[3.1.0]hexanones 2l–n in low yields. However, the yield was improved by the addition of copper(II) acetate as a co-oxidant during the reaction (entries 15–17). In addition, the azabicyclo[3.1.0]hexanone 2o was obtained in a poor yield as a 17:6 diastereoisomeric mixture along with tetrahydrofuro[3,4-c]pyrrol-4-one 5 (entry 18). The oxidation of butanamide 1p having no substituent at the olefin terminal produced the corresponding 4-methylpyrrolidinone 6p (entry 19). Use the manganese(III)–copper(II) system at room temperature led to the formation of the corresponding azabicyclo[3.1.0]hexanone 2p having no substituent at the C-6 position, but in a low yield (entry 20). The oxidation of the ester 1q was significantly affected by the solvent. When the reaction was carried out in acetic acid, the corresponding azabicyclo[3.1.0]hexanone was not produced, but the pyrrolidinones 3q and 7q were obtained (entry 21). However, a similar reaction in ethanol afforded the desired azabicyclo[3.1.0]hexanone 2q (entry 22). The reaction of 1r in ethanol became messy and an intractable mixture was obtained. However, the isopropenylpyrrolidinone 8 was isolated by the manganese(III)–copper(II)-mediated oxidation in acetic acid (Scheme 1).

We next investigated the deprotection of the nitrogen-protective group on the azabicyclo[3.1.0]hexanones 2 since many biologically active azabicyclo[3.1.0]hexanes have no substituent on the nitrogen atom and the direct preparation of 12 was not effective under the stated reaction conditions (entry 13). The deprotection of the tertiary butyl group of 2g was conducted under acidic conditions, for example, 60% aqueous perchloric acid in acetonitrile, and concentrated hydrochloric acid in acetonitrile, however, the reaction became complex and none of the desired deprotected compound 2j was detected. The hydrogenolysis of the benzyl group of 2a was also examined in the presence of palladium-activated carbon and formic acid as a hydrogen donor. Unfortunately, the reduction of the highly strained cyclopropane moiety preferentially occurred instead of the benzyl group, giving the ring-opened pyrrolidinone 6a (Scheme 2). A similar reduction under a hydrogen atmosphere (50 atm) also gave a similar result. As the reductive deprotection failed, we next attempted the oxidative deprotection of the p-methoxybenzyl (PMB) group. The PMB group of 2h was successfully removed by oxidation with cerium(IV) ammonium nitrate (CAN) to give the deprotected azabicyclohexanone 2j in a 67% yield together with the oxidation product 2h' (22%), which could be converted into the desired 2j by the methanolysis in the presence of potassium carbonate (Scheme 2).

Scheme 1

Scheme 2

Although the synthesis of 3-oxabicyclo[3.1.0]hexan-2-ones using the manganese(III)–copper(II)-based oxidation of 2j...
propenyl 3-oxobutanoates is known,\textsuperscript{7a,b,d–f} we also reported the manganese(III) oxidation of 3,3-diphenylprop-2-enyl 3-oxobutanoate (9a) in acetic acid, mainly affording a decomposition product together with a trace amount of 3,7-dioxabicyclo[3.3.0]oct-8-en-2-one.\textsuperscript{13} Since we have established the convenient route to the azabicyclo[3.3.0]hexanones \textsuperscript{2} from N-propenyl-3-oxobutanamides 1 (vide supra), we reconsidered the reaction of 3-oxobutanoate 9a as an analogue of 1. The reaction of 9a was carried out under the conditions established in the reaction of 1 to successfully give the desired 3-oxabicyclo[3.1.0]hex-2-one 10a (48%) albeit with the recovery of 9a (24%) (Table 2, entry 1). In order to improve the yield, we examined several reaction conditions, for example, the reaction in acetic acid, isopropyl alcohol, or benzene; using manganese(III) picolinate in dimethylformamide instead of manganese(III) acetate; or adding potassium acetate as a buffer.\textsuperscript{6} Although all attempts failed, using 6 equivalents of manganese(III) acetate led to the complete consumption of 9a and a maximum yield of 10a (64%) (entry 4).

Other 3-oxobutanoates 9b–d also displayed a similar behavior to produce the corresponding 3-oxabicyclo[3.1.0]hexanones 10b–d (entries 6–8). Since Bertrand et al. reported the reaction of 9e,\textsuperscript{7a} we repeated the same reaction of 9e from the standpoint of the reaction mechanism. Unfortunately, we could not reproduce the yield of 10e (entry 10) even though a previous study achieved a 57% yield of 10e. Under our reaction conditions, the reaction of 9e barely afforded 10e in 28% yield (entry 12).

A similar reaction of the S-propenyl 3-oxobutanethioates 11a–d in ethanol gave the desired 3-thiabicyclo[3.1.0]hexan-2-ones 12a–d in moderate yields except for the reaction of 11e (entry 12). For comparison with the reaction in ethanol, the reaction of 11a–d was conducted in acetic acid. As a result, dihydrothieno[3,4-c]furanone 13a–d and dihydrothiophenones 15a–d were mainly obtained (entries 5–8). The structure of the products 12–16 was well characterized by spectroscopic methods and elemental analyses except for 14b, 14c, 15a, 15b, and 15d, which was deduced by comparison of the spectroscopic data with those of 14a,d and 15c.

### Table 2 Oxidation of Propenyl 3-Oxobutanoates 9a–e with Manganese(III) Acetate Dihydrate\textsuperscript{a}

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\textsuperscript{a}The oxidation of 9 (0.5 mmol) with Mn(OAc)\textsubscript{3}·2H\textsubscript{2}O was carried out in EtOH (20 mL) at reflux temperature. Before the reaction, the mixture was degassed under reduced pressure for 30 min using an ultrasonicator followed by argon displacement.

\textsuperscript{b}Oxobutanoate 9/Mn(OAc)\textsubscript{3}·2H\textsubscript{2}O.

\textsuperscript{c}Recovery of 9.

\textsuperscript{d}Isolated yield based on the amount of 9 used.

\textsuperscript{e}Cu(OAc)\textsubscript{2} (0.60 mmol) as a co-oxidant was also added.

\textsuperscript{f}The oxidation of 9e (1 mmol) was carried out in AcOH (20 mL) at 75 °C.

\textsuperscript{g}The oxidation of 9e (4 mmol) was conducted in AcOH (10 mL) at 75 °C in the presence of Cu(OAc)\textsubscript{2} (4 mmol) and KOAc (16 mmol) in air.

\textsuperscript{h}Cu(OAc)\textsubscript{2} (1.5 mmol) and KOAc (2.5 mmol) were added as buffers.
The plausible pathway for the formation of the bicyclo[3.1.0]hexan-2-ones 2, 10, and 12 could be explained by the previously proposed mechanism (Scheme 3). The formation of the manganese(III)-enolate complex is the key step in the oxidation. The complex A undergoes the oxidative 5-exo-trig cyclization to give the exomethyl radicals B followed again by enolization with manganese(III) at the 1,3-dicarbonyl moiety, affording radicals C. It was suggested that two possible and reasonable routes to the final bicyclo[3.1.0]hexan-2-ones 2, 10, and 12 from the radicals C would be present. When the intramolecular cyclization accompanied by the one-electron transfer oxidation would occur, the final products 2, 10, and 12 would be produced (path A), while the tertiary carbon radicals C (R = aryl group) would undergo the manganese(III) oxidation to produce the same products during the ionic cyclization process (path B). Since the tertiary carbon radicals C (R = aryl group), except for the primary and secondary radicals produced from 10, 11, and 9e are easily oxidized by manganese(III), the path B should be favored. However, the result of the reaction using prop-2-enyl 3-oxobutanate (9e) supported path A since the oxidation actually afforded the corresponding bicyclo[3.1.0]hexanone 10e even in the absence of copper(II) acetate (Table 2, entries 9 and 11). In general, it is known that the terminal methyl radicals B (R = H and X = O) generated by the oxidative cyclization of the enolate complex between 9e and manganese(III) cannot be oxidized to form the corresponding primary cation D without the assistance of copper(II) acetate. Therefore, the ionic cyclization in path B must be ruled out in the case of 9e.

When the reaction was carried out in the presence of copper(II) acetate as a co-oxidant, the yield of the bicyclo[3.1.0]hexanones was improved. This also supported the path B rather than the path A. Bertrand et al. also suggested a similar reaction pathway using the manganese(III)–copper(II) combination. Moreover, Yang et al. demonstrated the bicyclo[3.1.0]hexan-2-one 11 via the ionic process using the isopropyl bromide, which was synthetically equivalent of the tertiary carbocation D albeit under basic conditions (Scheme 4). When the reaction was carried out in acetic acid, the pyrrolidinones 3, dihydrothienofuranones 13, and dihydrothiophenones 15 were preferentially formed rather than the corresponding bicyclohexanones 2 and 12. It is suggested that the tertiary carbon radicals C should be easily oxidized via the electron-transfer oxidation process by metal oxidants since the reflux temperature of acetic acid is higher than that of ethanol.

### Table 3 Oxidation of S-Propenyl 3-Oxobutanethioates 11a–d with Manganese(III) Acetate Dihydrate

<table>
<thead>
<tr>
<th>Entry</th>
<th>11</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Molar ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Solvent</th>
<th>Time (min)</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11a</td>
<td>Ph</td>
<td>1:4.5</td>
<td>EtOH</td>
<td>10</td>
<td>58</td>
<td>8</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>11b</td>
<td>4-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1:6.5</td>
<td>EtOH</td>
<td>30</td>
<td>trace</td>
<td>21</td>
<td>23</td>
<td>14</td>
<td>(16b)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11c</td>
<td>4-CIC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1:5.5</td>
<td>EtOH</td>
<td>15</td>
<td>51</td>
<td>8</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>11d</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1:5.5</td>
<td>EtOH</td>
<td>20</td>
<td>37</td>
<td>12</td>
<td>17</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>11a</td>
<td>Ph</td>
<td>1:3.5</td>
<td>AcOH</td>
<td>0.5</td>
<td>–</td>
<td>33</td>
<td>–</td>
<td>–</td>
<td>30</td>
<td>(15a)</td>
</tr>
<tr>
<td>6</td>
<td>11b</td>
<td>4-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1:4.5</td>
<td>AcOH</td>
<td>1</td>
<td>–</td>
<td>28</td>
<td>–</td>
<td>19</td>
<td>(15b)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>11c</td>
<td>4-CIC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1:4.5</td>
<td>AcOH</td>
<td>1.5</td>
<td>6</td>
<td>35</td>
<td>–</td>
<td>22</td>
<td>(15c)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>11d</td>
<td>4-FC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>1:4.5</td>
<td>AcOH</td>
<td>10</td>
<td>4</td>
<td>21</td>
<td>–</td>
<td>30</td>
<td>(15d)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>The oxidation of 11 (0.5 mmol) with Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O was carried out in EtOH (30 mL) or AcOH (20 mL) at reflux temperature. Before starting the reaction, the mixture was degassed under reduced pressure for 30 min using an ultrasonicator followed by argon displacement.

<sup>b</sup>3-Oxobutanethioate 11/Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O.

<sup>c</sup>Isolated yield based on the amount of 11 used.
In conclusion, we have developed the convenient synthesis for the 3-aza- 2, 3-oxa- 10, and 3-thiabicyclo[3.1.0]hexan-2-ones 12 using the oxidation of simple N-propenyl-3-oxobutanamides 1, propenyl 3-oxobutanoates 9, and S-propenyl 3-oxobutanes 11 with manganese(III) acetate in ethanol. The use of ethanol as a solvent promoted the production of the desired bicyclo[3.1.0]hexan-2-ones. Although the synthesis of the 6,6-diaryl-substituted 3-azabicyclo[3.1.0]hexan-2-ones 2 was achieved, the yield of 2o and 2p bearing a mono and no substituent at the C-6 position, respectively, was poor. Furthermore, the N-3-methylbut-2-enyl-3-oxobutananamide 1r did not afford any bicyclo[3.1.0]hexan-2-ones. For the plausible pathway for the formation of the bicyclo[3.1.0]hexan-2-ones 2, 10, and 12, the oxidative radical cyclopropanation in the absence of copper(II) acetate as a co-oxidant is proposed.

The NMR spectra were recorded using a JNM AL300 FT NMR spectrometer at 300 MHz for 1H and at 75 MHz for 13C, with TMS as the internal standard. The chemical shifts are reported in δ values (ppm). The IR spectra of neat samples were measured by the ATR method using a Shimadzu 8400 FTIR spectrophotometer and MIR-acle A, and expressed in cm⁻¹. The EI MS spectra were recorded on a Shimadzu QP-5050A GC–MS instrument with an ionizing voltage of 70 eV. The high-resolution mass spectra were measured at the Institute for Materials Chemistry and Engineering, Kyushu University, Fukuoka, Japan. The elemental analyses were performed at the Instrumental Analysis Center, Kumamoto University, Kumamoto, Japan. Mn(OAc)₃·2H₂O was purchased from Wako Pure Chemical Ind., Ltd. Mn(OAc)₃·2H₂O was prepared according to the method described in the literature. 4,5 N-(3,3-Diarylprop-2-enyl)-3-oxobutanamides 1 a-g and 11 a-n were prepared by the reaction of the diketene with the corresponding 3,3-diarylprop-2-enamines obtained by the reaction of the 1,1-diaryl-1-bromoprop-1-enes with amines. 17,18 The 3-oxobutanamides 1 p.r were also prepared by a similar method. N-(3,3-Diarylprop-2-enyl)-3-oxobutanamides 1b were prepared by the reaction of 4-methoxybenzaldehyde with 3,3-dipropylprop-2-en-1-amine followed by reduction with NaBH₄ in absolute MeOH. 19 The 3-oxobutanamides 1 o.p were synthesized by the reaction of the diketene with N-benzyl-(3-phenylprop-2-enyl)amine and allylbenzylamine, 20 respectively. Ethyl N-benzyl-N-(3,3-dipropylprop-2-enyl)malonate (1q) was prepared by the condensation of N-benzyl-3,3-dipropylprop-2-enylamine with ethyl hydrogen malonate. The 3-oxobutanamides 9 a-d were prepared by the reaction of the diketene with the corresponding propenethiols, which were obtained by the reduction of the 3,3-diarylpropenoates 18, 3-Oxobutanoate 9e was prepared according to the literature. 21 The S-propenyl 3-oxobutanes 11 a-d were prepared by the reaction of the diketene with the corresponding propenethiols, which were obtained by the reduction of the 3,3-diarylpropenoates 18 followed by bromination with PBr₃, thioestrafication with KSAc, 22 and further reduction with LiAlH₄.

Oxidation of N-Propenyl-3-oxobutanamides 1, Propenyl 3-Oxobutanamides 9, and S-Propenyl 3-Oxobutanes 11: General Procedure

A 1,3-dicarboxyl compound 1, 9, or 11 (0.5 mmol) and a solvent (20 mL) were placed in a 50 mL flask. Before starting the reaction, the mixture was degassed under reduced pressure for 30 min using an ultrasonicator and then filled with argon. Mn(OAc)₃·2H₂O was quickly added and then the mixture was heated under reflux until the brown color of Mn(III) had disappeared. The molar ratios and the reaction times are shown in Tables 1 – 3. When EtOH was used as the solvent, the solvent was removed in vacuo, and the residue was triturated with H₂O followed by extraction with CHCl₃ (3 × 10 mL). When AcOH was used, H₂O (80 mL) was added to the resulting solution, and the aqueous solution was extracted with CHCl₃ (3 × 5 mL). The combined organic extracts were dried (MgSO₄) and then concentrated to dryness. The products were separated by a silica gel TLC (Wakogel B-10) eluting with CHCl₃. The products were further purified by recrystallization from appropriate solvents.
1-Acetyl-3-benzyl-6,6-diphenyl-3-azabicyclo[3.1.0]hexan-2-one (2a)

\[ R_{f} = 0.42 \] (CHCl₃-MeOH, 98:2); colorless prisms (Et₂O-hexane); mp 132 °C.

IR (KBr): 1697, 1682 cm⁻¹ (C=O).

\[ ^{1}H \text{ NMR (CDCl₃)}: \delta = 7.41-7.08 (13 \text{ H arom}, m), 6.62-6.60 (2 \text{ H arom}, m), 4.03 (1 \text{ H, d}, J = 14.7 Hz, PhCH₃), 3.80 (1 \text{ H, d}, J = 14.7 Hz, PhCH₃), 3.43 (1 \text{ H, dd}, J = 11.0, 6.4 Hz, H-4), 3.33 (1 \text{ H, br d}, J = 6.4 Hz, H-5), 2.99 (1 \text{ H, br d}, J = 11.0 Hz, H-4), 2.65 (3 \text{ H, s}, COCH₃).

\[ ^{13}C \text{ NMR (CDCl₃)}: \delta = 200.4, 168.8 (2 \text{ C, C}=O), 138.6, 136.7, 135.2 (3 \text{ C arom}), 129.0, 128.9, 128.4, 128.4, 128.3, 127.9, 127.5, 127.3, 127.2 (15 \text{ CH₃}), 52.5, 50.6 (2 \text{ C, C-1, C-6), 46.4 (PhCH₃), 44.2 (C-4), 30.3 (COCH₃).}

FAB HRMS (acetone-NBA): m/z: calcd for C₂₀H₁₉NO₂: 323.1344; found: 323.1344.

IR (KBr): 1697, 1676 cm⁻¹ (C=O).

\[ ^{1}H \text{ NMR (CDCl₃)}: \delta = 7.42-7.11 (10 \text{ H arom}, m), 3.89 [1 \text{ H, hept}, J = 6.8 Hz, NCH(CH₃)₂], 3.52 (1 \text{ H, dd}, J = 11.0, 6.4 Hz, H-4), 3.33 (1 \text{ H, br d}, J = 6.4 Hz, H-5), 3.11 (1 \text{ H, br d}, J = 11.0 Hz, H-4), 2.62 (3 \text{ H, s}, COCH₃), 0.93 [6 \text{ H, d}, J = 6.8 Hz, NCH(CH₃)₂].

\[ ^{13}C \text{ NMR (CDCl₃)}: \delta = 200.7, 167.8 (2 \text{ C, C}=O), 138.7, 136.8 (2 \text{ C arom}), 129.1, 128.9, 128.4, 127.5, 127.3 (10 \text{ CH₃}), 52.9, 49.9 (2 \text{ C, C-1, C-6), 42.1 [NCH(CH₃)₂], 39.3 (C-4), 30.4 (COCH₃), 26.1 (C-5), 19.3, 18.0 [2 \text{ C, C(NCH₃)₂}].


1-Acetyl-3-isopropyl-6,6-diphenyl-3-azabicyclo[3.1.0]hexan-2-one (2b)

\[ R_{f} = 0.22 \] (CHCl₃); colorless needles (Et₂O-hexane); mp 165–166 °C.

\[ ^{1}H \text{ NMR (CDCl₃)}: \delta = 7.24-7.14 (10 \text{ H arom}, m), 2.40 (1 \text{ H, d}, J = 7.4 Hz, H-4), 2.19 (3 \text{ H, s}, COCH₃), 2.17 (3 \text{ H, s}, COCH₃).

\[ ^{13}C \text{ NMR (CDCl₃)}: \delta = 200.0, 168.6 (2 \text{ C, C}=O), 138.6, 138.8 (2 \text{ C arom}), 129.0, 128.9, 128.4, 127.5, 127.3 (10 \text{ CH₃}), 52.6, 50.0 (2 \text{ C, C-1, C-6), 44.6, 44.0 (2 \text{ C, C-4, NCH₂CH₂CH₃), 30.4 (COCH₃), 26.5 (C-5), 19.4 (NCH₂CH₂CH₃), 11.1 (NCH₂CH₃).}


Synthesis 2009, No. 3, 409–423 © Thieme Stuttgart · New York
1\(^1\)H NMR (CDCl3); \(\delta = 7.40–7.09 \text{ (10 H arom)}, 6.64 \text{ (2 H arom, d, } J = 8.4 \text{ Hz)}, 6.54 \text{ (2 H arom, d, } J = 8.4 \text{ Hz)}, 3.95 \text{ (1 H, dd, } J = 14.7 \text{ Hz, 4-MeOC}_6\text{H}_4\text{C}_2\text{H}_4\text{)}, 3.75 \text{ (1 H, d, } J = 14.7 \text{ Hz, 4-MeOC}_6\text{H}_4\text{C}_2\text{H}_4\text{)}, 3.72 \text{ (3 H, s, OCH}_3\text{)}, 3.41 \text{ (1 H, dd, } J = 11.0, 6.2 \text{ Hz, H-4)}, 3.31 \text{ (1 H, br d, } J = 6.2 \text{ Hz, H-5}), 2.96 \text{ (1 H, br d, } J = 11.0 \text{ Hz, H-4)}, 2.64 \text{ (3 H, s, COCH}_3\text{)}.

1\(^1\)C NMR (CDCl3); \(\delta = 200.3, 168.6 \text{ (2 C, C=O)}, 158.6, 138.6, 136.7 \text{ (3 C arom)}, 129.1, 128.6, 128.8, 128.4, 128.3, 127.4 \text{ (11 CH arom)}, 127.22 \text{ (C arom)}, 127.16 \text{ (CH arom)}, 113.7 \text{ (2 CH arom)}, 55.0 \text{ (OCH}_3\text{)}, 52.5, 50.4 \text{ (2 C, C-1, C-6), 45.7 (4-MeOC}_6\text{H}_4\text{C}_2\text{H}_4\text{)}, 44.0 \text{ (C-4), 30.2 (COCH}_3\text{)}, 26.5 \text{ (C-5)}.

Anal. Calcd for C\(_{19}\)H\(_{17}\)NO\(_2\)·3\(\frac{1}{8}\)H\(_2\)O: C, 76.52; H, 6.00; N, 4.70. Found: C, 76.81; H, 6.08; N, 3.33.

**1-Acetyl-3,6,6-triphenyl-3-azabicyclo[3.1.0]hexan-2-one (2l)**

R\(_f\) = 0.47 (CHCl\(_3\)-MeOH, 98:2); colorless needles (Et\(_2\)O-hexane); mp 141.0 °C.

IR (KBr): 1701, 1684 cm\(^{-1}\) (C=O).

1\(^1\)H NMR (CDCl\(_3\)); \(\delta = 7.27–7.07 \text{ (11 H arom)}, 6.66–6.63 \text{ (2 H arom, m)}, 4.13 \text{ (1 H, d, } J = 14.5 \text{ Hz, PhCH}_3\text{)}, 3.86 \text{ (1 H, d, } J = 14.5 \text{ Hz, PhCH}_3\text{)}, 3.48 \text{ (1 H, dd, } J = 11.0, 6.4 \text{ Hz, H-4)}, 3.28 \text{ (1 H, br d, } J = 6.4 \text{ Hz, H-5}), 2.99 \text{ (1 H, br d, } J = 11.0 \text{ Hz, H-4)}, 2.64 \text{ (3 H, s, COCH}_3\text{)}.

1\(^1\)C NMR (CDCl\(_3\)); \(\delta = 199.8, 168.1 \text{ (2 C, C=O)}, 136.7, 134.8, 134.7, 133.7, 133.3 \text{ (5 C arom)}, 130.1, 129.6, 129.3, 128.7, 128.4, 128.0, 127.4 \text{ (13 CH arom)}, 52.2, 49.1 \text{ (2 C, C-1, C-6), 46.5 (PhCH}_3\text{)}, 43.9 \text{ (C-4), 30.3 (COCH}_3\text{)}, 27.0 \text{ (C-5)}.

Anal. Calcd for C\(_{25}\)H\(_{21}\)NO\(_2\): C, 81.72; H, 5.76; N, 3.81. Found: C, 81.90; H, 5.83; N, 3.79.

**1-Acetyl-3,6-diphenyl-3-azabicyclo[3.1.0]hexan-2-one (2i)**

R\(_f\) = 0.36 (CHCl\(_3\)-MeOH, 98:2); colorless prisms (Et\(_2\)O-hexane); mp 94–96 °C.

IR (KBr): 1695, 1682 cm\(^{-1}\) (C=O).

1\(^1\)H NMR (CDCl\(_3\)); \(\delta = 7.51–6.81 \text{ (15 H arom)}, 4.11 \text{ (1 H, dd, } J = 11.0, 6.2 \text{ Hz, H-4)}, 3.54 \text{ (1 H, br d, } J = 11.0 \text{ Hz, H-5}), 3.18 \text{ (1 H, br d, } J = 11.0 \text{ Hz, H-4}), 2.55 \text{ (3 H, s, COCH}_3\text{)}.

1\(^1\)C NMR (CDCl\(_3\)); \(\delta = 200.2, 172.1 \text{ (2 C, C=O)}, 138.5, 136.9 \text{ (2 C arom)}, 129.0, 128.9, 128.6, 128.5, 127.7, 127.5, 125.7, 121.9 \text{ (15 CH arom)}, 52.9, 50.4 \text{ (2 C, C-1, C-6), 46.7 (C-4), 30.4 (COCH}_3\text{)}, 26.0 \text{ (C-5)}.

Anal. Calcd for C\(_{28}\)H\(_{27}\)NO\(_2\): C, 82.12; H, 6.71; N, 3.44. Found: C, 82.27; H, 6.71; N, 3.44.
1H NMR (CDCl3): δ = 7.36–7.06 (8 H arom, m), 6.57–6.55 (2 H arom, m), 4.03 (1 H, d, J = 14.7 Hz, PhCH3), 3.81 (1 H, d, J = 10.3, 5.9 Hz, H-4), 3.12 (1 H, br d, J = 10.3 Hz, H-4), 2.62 (3 H, s, COCH3), 2.38 (1 H, d, J = 7.7, 5.9, 5.1 Hz, H-5), 1.92 (1 H, d, J = 7.7, 4.0 Hz, H-6), 1.09 (1 H, d, J = 5.1, 4.0 Hz, H-6).

13C NMR (CDCl3): 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2 (15 CH arom), 61.4 (OCH2CH3), 47.5 (C-1), 46.6 (PhCH3), 45.2 (C-6), 44.2 (C-4), 27.2 (C-5), 13.8 (OCH3).

Anal. Calcd for C28H30NO2: C, 78.66; H, 6.84; N, 3.28. Found: C, 78.81; H, 6.12; N, 3.40.

4-(Acetoxyphenylmethyl)-3-acyl-1-benzylpyrrolidin-2-one (3b)

IR (KBr): 1695, 1684 cm−1 (C=O).

Rf = 0.31 (CHCl3–MeOH, 98:2); colorless prisms (Et2O–hexane); mp 161–162 °C.

IR (KBr): 3600–3200 (OH), 1709, 1670 cm−1 (C=O).

13C NMR (CDCl3): 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2 (15 CH arom), 61.4 (OCH2CH3), 47.5 (C-1), 46.6 (PhCH3), 45.2 (C-6), 44.2 (C-4), 27.2 (C-5), 13.8 (OCH3).

FAB MS: m/z (%) = 410 (100, M – 59), 367 (16), 195 (37), 91 (42).

IR (KBr): 1744, 1717, 1688 cm−1 (C=O).

1H NMR (CDCl3): δ = 7.27–7.04 (13 H arom, m), 4.43 (1 H, ddd, J = 8.8, 3.7, 3.7 Hz, H-3), 3.43 (1 H, d, J = 14.7 Hz, PhCH3), 3.89 (1 H, d, J = 3.7 Hz, H-4), 3.88 (1 H, d, J = 14.7 Hz, PhCH3), 3.47 (1 H, d, J = 10.6, 8.8 Hz, H-2), 3.38 (1 H, d, J = 10.6, 3.7 Hz, H-2), 2.31 (9 H, br s, SOCH3, 2 × CH2), 2.02 (3 H, s, COCH3).

13C NMR (CDCl3): 138.4, 137.6, 137.0, 137.4, 135.4 (5 C arom), 128.1, 128.1, 128.0, 127.9, 127.5, 127.1, 126.9 (13 CH arom), 87.1 (AcO), 59.0 (C-4), 47.7 (C-2), 46.5 (PhCH3), 39.6 (C-3), 30.1 (COCH3), 22.1 (OCH3).

FAB MS: m/z (%) = 220 (1, 2 × CH2).

In order to further characterize 3k, the pyrrolidinone 3k (0.05 mmol) was hydrolyzed with aq 10% H2SO4 (2 mL) in AcOH (4 mL). After stirring the mixture for 2 h at r.t. in air, H2O (10 mL) was added and the aqueous phase was extracted with CHCl3 (3 × 5 mL). The combined CHCl3 extracts were dried (MgSO4), and then concentrated to dryness. The corresponding alcohol 3k was obtained in 95% yield, which was further purified by recrystallization from EtOH–hexane.

3-Acetyl-1-benzyl-4-[hydroxybis(4-methylphenyl)methyl]pyrrolidin-2-one (3k)
Ethyl 4-(Acetoxypiphenylmethyl)-1-benzyl-2-oxopyrrolidine-3-carboxylate (3q)

\[ R_1 = 0.27 \text{ (CHCl}_3\text{); colorless oil.} \]

IR (KBrs): 1742, 1697 cm\(^{-1}\) (C=O).

\(^1\)H NMR (CDCl\(_3\)): \( \delta = 7.27-7.19 \text{ (13 H arom, m)} \), 7.02-7.00 (2 H arom, m), 4.53 (1 H, ddd, \( J = 8.8, 4.0, 3.7 \text{ Hz, H-4} \)), 4.38 (1 H, d, \( J = 14.7 \text{ Hz, PhCH}_2\)), 4.19 (2 H, q, \( J = 7.0 \text{ Hz, OCH}_2\text{CH}_3\)), 3.77 (1 H, d, \( J = 14.7 \text{ Hz, PhCCH}_3\)), 3.75 (1 H, d, \( J = 4.0 \text{ Hz, H-3} \)), 3.67 (1 H, d, \( J = 10.6, 8.8 \text{ Hz, H-5} \)), 3.31 (1 H, ddd, \( J = 10.6, 3.7 \text{ Hz, H-5} \)), 2.04 (3 H, s, OCOCH\(_3\)), 1.27 (3 H, t, \( J = 7.0 \text{ Hz, OCH}_2\text{CH}_3\)).

FAB HRMS (acetone–NBA): \( m/z \) calcd for C\(_{22}\)H\(_{26}\)NO\(_3\): 458.1913 (M + 1); found: 458.2289.

3-Acetyl-1-benzyl-4-ethoxy-4-methylpyrrolidin-2-one (6p)

\[ R_1 = 0.30 \text{ (CHCl}_3\text{); colorless oil.} \]

IR (KBrs): 1715, 1684 cm\(^{-1}\) (C=O).

\(^1\)H NMR (CDCl\(_3\)): \( \delta = 7.35-7.20 \text{ (5 H arom, m)} \), 4.47 (1 H, d, \( J = 14.7 \text{ Hz, PhCH}_2\)), 4.40 (1 H, d, \( J = 14.7 \text{ Hz, PhCH}_2\)), 3.40 (1 H, d, \( J = 8.8, 7.3 \text{ Hz, H-5} \)), 3.24 (1 H, d, \( J = 7.0 \text{ Hz, H-3} \)), 2.89-2.75 (2 H, m, H-4, H-5), 2.45 (3 H, s, COCH\(_3\)), 1.06 (3 H, d, \( J = 7.0 \text{ Hz, HCH}_3\)).

FAB HRMS (acetone–NBA): \( m/z \) calcd for C\(_{18}\)H\(_{22}\)NO\(_2\): 232.1338 (M + 1); found: 232.1332.

Ethyl 1-Benzyl-4-(hydroxypiphenylmethyl)-2-oxopyrrolidine-3-carboxylate (7q)

\[ R_1 = 0.13 \text{ (CHCl}_3\text{); colorless microcrystals (CHCl}_3\text{–hexane); mp 146°C.} \]

IR (KBrs): 3200–3500 (OH), 1732, 1674 cm\(^{-1}\) (C=O).

\(^1\)H NMR (CDCl\(_3\)): \( \delta = 7.42-7.13 \text{ (15 H, m)} \), 4.46 (1 H, d, \( J = 15.0 \text{ Hz, PhCH}_2\)), 4.33 (1 H, d, \( J = 15.0 \text{ Hz, PhCH}_2\)), 4.04–3.87 (3 H, m, H-4, OCH\(_2\)CH\(_3\)), 3.66 (1 H, d, \( J = 7.0 \text{ Hz, H-3} \)), 3.42 (1 H, d, \( J = 10.3, 9.2 \text{ Hz, H-5} \)), 3.17 (1 H, ddd, \( J = 10.3, 6.2 \text{ Hz, H-5} \)), 2.90 (1 H, br s, OH), 1.09 (3 H, t, \( J = 7.0 \text{ Hz, OCH}_2\text{CH}_3\)).

FAB HRMS (acetone–NBA): \( m/z \) calcd for C\(_{22}\)H\(_{25}\)NO\(_3\): 352.1913 (M + 1); found: 352.1913.

5-Benzyl-3-etoxy-3-methyl-1-phenyl-1H-tetrahydrofuro[3,4-c]pyrrol-4(5H)-one (5)

\[ R_1 = 0.13 \text{ (CHCl}_3\text{); colorless oil.} \]

IR (KBrs): 1630 cm\(^{-1}\) (C=O).

\(^1\)H NMR (CDCl\(_3\)): \( \delta = 7.38-7.25 \text{ (10 H arom, m)} \), 4.68 (1 H, d, \( J = 14.7 \text{ Hz, PhCH}_2\)), 4.65 (1 H, d, \( J = 5.9 \text{ Hz, H-1} \)), 4.33 (1 H, d, \( J = 14.7 \text{ Hz, PhCH}_2\)), 3.62–3.49 (2 H, m, OCH\(_2\)CH\(_3\)), 3.40 (1 H, dd, \( J = 10.3, 6.2 \text{ Hz, H-6} \)), 3.28–3.17 (2 H, m, H-3a, H-6a), 3.10 (1 H, br d, \( J = 10.3 \text{ Hz, H-6} \)), 1.75 (3 H, s, CH\(_3\)), 1.08 (3 H, t, \( J = 7.0 \text{ Hz, OCH}_2\text{CH}_3\)).

FAB HRMS (acetone–NBA): \( m/z \) calcd for C\(_{22}\)H\(_{28}\)NO\(_3\): 340.1666 (M + 1); found: 340.1610.

Hydrogenolysis of 2a in the Presence of Palladium-Activated Carbon; 3-Acetyl-1-benzyl-4-diphenylmethylpyrrolidin-2-one (6a)

To a solution of 2a (0.2 mmol) in formic acid–MeOH (5:95, 20 mL) was added 10% Pd/C (100 mg) and the mixture was stirred for 15 h at r.t. under argon in a dark room. The resulting mixture was filtered...
by a Celite column to remove Pd/C, and the filtrate was concentrated to dryness. The obtained residue was triturated with H2O followed by extraction with CHCl3, (3 × 5 mL). The combined CHCl3 extracts were dried (MgSO4) and concentrated to dryness, giving the ring-opened pyrrolidinone 6a in a quantitative yield; Rf = 0.24 (CHCl3); colorless oil.

IR (KBr): 1717, 1684 cm⁻¹ (C=O).

1H NMR (CDCl3): δ = 7.34–7.11 (15 H arom, m), 4.40 (1 H, d, J = 14.7 Hz, PhCH3), 4.34 (1 H, d, J = 14.7 Hz, PhCH3), 3.81 (1 H, ddd, J = 12.1, 8.4, 5.5, 1.1 Hz, H-4), 3.66 (1 H, d, J = 12.1 Hz, CPhH3), 3.47 (1 H, d, J = 5.5 Hz, H-3), 3.36 (1 H, dd, J = 9.9, 8.4 Hz, H-5), 2.86 (1 H, dd, J = 9.9, 5.1 Hz, H-5), 1.99 (3 H, s, CH3).

13C NMR (CDCl3): δ = 198.6, 169.1 (2 C, C=O), 142.3, 141.8, 135.7 (3 C arom), 128.7, 127.94, 127.89, 127.62, 127.56, 126.9, 126.5 (18 CHPh2), 61.0 (C-3), 56.4 (PhH3).

Oxidative Deprotection of p-Methoxybenzyl (PMB) Group of 2h Using CAN

The 3-azabicyclo[3.1.0]hexan-2-one 2h (0.3 mmol) was dissolved in MeCN–H2O (1:2, 10 mL) and the solution was cooled to 0 °C followed by adding cerium(IV) ammonium nitrate (CAN) (1.05 mmol, 3.5 equiv). After stirring 30 min at 0 °C, EtOAc (5 mL) and aq sat. NaHCO3 (20 mL) were added to the mixture, and the resulting solution was extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were (MgSO4) and concentrated to dryness. The obtained residue was triturated with H2O followed by a Celite column to remove Pd/C, and the filtrate was concentrated to dryness. The obtained residue was triturated with H2O followed by extraction with CHCl3, (3 × 5 mL). The combined CHCl3 extracts were (MgSO4) and concentrated to dryness, giving the ring-opened pyrrolidinone 6a in a quantitative yield; Rf = 0.24 (CHCl3); colorless oil.

IR (KBr): 1717, 1684 cm⁻¹ (C=O).

1H NMR (CDCl3): δ = 7.30–7.01 (8 H arom, m), 4.41 (1 H, dd, J = 9.9, 5.5 Hz, H-4), 4.15 (1 H, br, d, J = 9.9 Hz, H-4), 3.67 (1 H, br, d, J = 5.5 Hz, H-5), 2.59 (3 H, s, COCH3), 2.30 (3 H, s, CH3), 2.23 (3 H, s, CH3).

13C NMR (CDCl3): δ = 197.9, 171.5 (2 C, C=O), 138.0, 137.6, 134.3, 133.0 (4 C arom), 130.1, 129.4, 128.6, 128.1 (8 CHPh2), 64.9 (C-4), 51.2, 50.7 (2 C, C-1, C-6), 31.9, 29.8 (2 C, COCH3, C-5), 21.1, 21.0 (2 C, CH3).


1-Acetyl-3-oxabicyclo[3.1.0]hexan-2-one (10e)7a

Rf = 0.22 (CHCl3); pale yellow microcrystals (Et2O–hexane); mp 184–186 °C.

IR (KBr): 1759, 1701 cm⁻¹ (C=O).

1H NMR (CDCl3): δ = 7.38–7.10 (8 H arom, m), 4.46 (1 H, dd, J = 10.3, 5.5 Hz, H-4), 4.11 (1 H, br, d, J = 10.3 Hz, H-4), 3.66 (1 H, br, d, J = 5.5 Hz, H-5), 2.59 (3 H, s, COCH3).

13C NMR (CDCl3): δ = 197.2, 170.9 (2 C, C=O), 135.3, 134.6, 134.1, 133.9 (4 C arom), 130.1, 129.9, 129.6, 129.1 (8 CHPh2), 64.7 (C-4), 50.4, 50.0 (2 C, C-1, C-6), 32.1, 29.8 (2 C, COCH3, C-5).

Anal. Calcd for C19H14O3·0.5H2O: C, 76.18; H, 5.52. Found: C, 76.14; H, 5.49.

1-Acetyl-3-oxabicyclo[3.1.0]hexan-2-one (10d)

Rf = 0.18 (CHCl3); colorless microcrystals (Et2O–hexane); mp 161–162 °C.

IR (KBr): 1769, 1693 cm⁻¹ (C=O).

1H NMR (CDCl3): δ = 7.41–6.91 (8 H arom, m), 4.46 (1 H, dd, J = 10.3, 5.5 Hz, H-4), 4.13 (1 H, br, d, J = 10.3 Hz, H-4), 3.67 (1 H, br, d, J = 5.5 Hz, H-5), 2.59 (3 H, s, COCH3).

13C NMR (CDCl3): δ = 197.3, 171.1 (2 C, C=O), 164.1, 163.7, 160.8, 160.4, 132.90, 132.85, 131.6, 131.5 (4 C arom), 130.5, 130.4, 130.1, 130.0, 116.9, 116.7, 116.0, 115.7 (8 CHPh2), 64.7 (C-4), 50.6, 50.0 (2 C, C-1, C-6), 32.1, 29.8 (2 C, COCH3, C-5).

Anal. Calcd for C19H16F2O3·0.5H2O: C, 69.51; H, 4.30. Found: C, 69.40; H, 4.41.

1-Acetyl-3-oxabicyclo[3.1.0]hexan-2-one (10e)7a

Rf = 0.15 (Et2O–hexane, 1:1); colorless oil.

IR (KBr): 1771, 1697 cm⁻¹ (C=O).

1H NMR (CDCl3): δ = 4.36 (1 H, d, J = 9.5, 4.7 Hz, H-4), 4.21 (1 H, br, d, J = 9.5 Hz, H-4), 2.85–2.79 (1 H, m, H-5), 2.58 (3 H, s, COCH3), 2.07 (1 H, dd, J = 8.1, 4.2 Hz, H-6), 1.44 (1 H, dd, J = 5.7, 4.2 Hz, H-6).

13C NMR (CDCl3): δ = 200.5, 172.7 (2 C, C=O), 67.1 (C-4), 36.4 (C-1), 29.8 (C-5), 29.2 (COCH3), 24.1 (C-6).

1-Acetyl-6,6-diphenyl-3-thiabicyclo[3.1.0]hexan-2-one (12a)

Rf = 0.49 (CHCl3); colorless microcrystals (Et2O–hexane); mp 130.0 °C.
IR (KBr): 1697 cm⁻¹ (C=O).

1H NMR (CDCl₃): δ = 7.47–7.12 (10 H arom), 3.76 (1 H, br d, J = 7.3 Hz, H-5), 3.71 (1 H, dd, J = 10.8, 7.3 Hz, H-4), 3.24 (1 H, br d, J = 10.8 Hz, H-4), 2.45 (3 H, s, CH₃), 2.43 (3 H, s, CH₃), 2.23 (3 H, s, CH₃).

13C NMR (CDCl₃): δ = 202.2, 198.1 (2 C, C=O), 138.2, 136.3 (2 C arom), 129.1, 128.7, 128.6, 128.4, 127.8, 127.6 (10 CH arom), 61.7 (C-1), 50.7 (C-6), 34.1 (C-5), 30.2 (COCH₃), 28.0 (C-4).

FAB HRMS (acetone–NBA): m/z calculated for C₁₂H₁₄O₂S: 207.0945 (M + 1); found: 207.0944.

1,1-Bis(4-chlorophenyl)-3-methyl-1,6a-dihydrothieno[3,4-c]furan-4(1H)-one (13c) Rf = 0.62 (CHCl₃); colorless oil.

IR (KBr): 1655 cm⁻¹ (C=O).

1H NMR (CDCl₃): δ = 7.45–7.38 (2 H arom, m), 7.18–6.96 (6 H arom, m), 4.91–4.83 (1 H, m, H-3a), 3.02 (1 H, dd, J = 10.3, 7.3 Hz, H-4), 2.67 (1 H, dd, J = 11.4, 10.3 Hz, H-4), 2.27 (3 H, d, J = 2.2 Hz, CH₃).

13C NMR (CDCl₃): δ = 189.2 (C=O), 157.8 (C-1), 141.7, 137.5, 134.5, 134.2 (4 C arom), 128.9, 127.8, 127.1 (8 CH arom), 113.3 (C-6a), 94.6 (C-4), 57.0 (C-3a), 34.1 (C-4), 12.9 (CH₃).

FAB HRMS (acetone–NBA): m/z calculated for C₁₉H₁₇Cl₂O₂S: 377.0170 (M + 1); found: 377.0177.

1,1-Bis(4-fluorophenyl)-3-methyl-1,6a-dihydrothieno[3,4-c]furan-4(1H)-one (13d) Rf = 0.58 (CHCl₃); colorless oil.

IR (KBr): 1665 cm⁻¹ (C=O).

1H NMR (CDCl₃): δ = 7.45–7.38 (2 H arom, m), 7.19–6.93 (6 H arom, m), 4.91–4.82 (1 H, m, H-3a), 3.02 (1 H, dd, J = 10.3, 7.3 Hz, H-4), 2.67 (1 H, dd, J = 11.4, 10.3 Hz, H-4), 2.27 (3 H, d, J = 2.2 Hz, CH₃).

13C NMR (CDCl₃): δ = 189.4 (C=O), 161.4, 163.9, 160.8, 160.6 (2 C arom), 158.0 (C-1), 139.3, 139.2, 135.1, 135.0 (2 C arom), 128.4, 128.3, 127.7, 127.5, 115.8, 115.5 (8 CH arom), 113.3 (C-6a), 94.9 (C-3), 57.3 (C-3a), 34.1 (C-4), 12.9 (CH₃).

FAB HRMS (acetone–NBA): m/z calculated for C₂₁H₂₁O₂S: 337.0761 (M + 1); found: 345.0750.
(1H, dd, J = 12.1, 9.9 Hz, H-4), 2.42 (3 H, s, CH₃), 2.31 (3 H, s, CH₃), 1.72 (3 H, s, CH₃), 0.80 (3 H, t, J = 7.0 Hz, OCH₂CH₃).

¹³C NMR (CDCl₃): δ = 197.5 (C=O), 142.8, 138.9, 136.9 (4 Cα⾃), 128.9, 128.8, 126.3, 126.0 (8 CH₂, 100.6 (C-6a), 84.3 (C-3), 66.3 (C-6a), 56.8 (OCH₂CH₃), 54.8 (C-3a), 32.6 (C-4), 21.1, 21.0, 20.8 (3 C, 3 × CH₃), 15.0 (OCH₂CH₃).

FAB MS: m/z (%) = 337 (100, M – 45), 277 (33), 211 (32), 195 (29), 119 (27).

1,1-Bis(4-chlorophenyl)-3-ethoxy-3-methyltetrahydrothieno[3,4-c]furan-4(1H)-one (14c)

Rf = 0.33 (CHCl₃–hexane, 1:1); colorless oil.

IR (KBr): 1746, 1722, 1688 cm⁻¹ (C=O).

¹⁷NMR (CDCl₃): δ = 7.35–7.14 (8 H arom, m), 4.65 (1 H, dd, J = 8.1, 3.7, 3.3 Hz, H-3), 3.88 (1 H, d, J = 3.7 Hz, H-4), 3.63 (1 H, dd, J = 12.1, 8.1 Hz, H-2), 3.36 (1 H, dd, J = 12.1, 3.3 Hz, H-2), 2.30 (3 H, s, COCH₃), 2.09 (3 H, s, COCH₃), 150 (CH₂).

FAB MS: m/z (%) = 377 (22, M – 59), 307 (37), 289 (18), 154 (100), 136 (77), 89 (12).

3-Ethoxy-1,1-bis(4-fluorophenyl)-3-methyltetrahydrothieno[3,4-c]furan-4(1H)-one (14d)

Rf = 0.71 (Et₂O–hexane, 1:1); colorless microcrystals (hexane); mp 172–173 °C.

IR (KBr): 1732 cm⁻¹ (C=O).

¹⁷NMR (CDCl₃): δ = 7.39–7.05 (8 H arom, m), 4.50 (1 H, dddd, J = 14.7, 12.5, 5.1 Hz, H-3a), 3.52–3.35 (2 H, m, OCH₂CH₃), 3.29 (1 H, dddd, J = 9.5, 5.1 Hz, H-4), 3.08 (1 H, d, J = 14.7 Hz, H-6a), 2.87 (1 H, dddd, J = 12.5, 9.9 Hz, H-4), 1.73 (3 H, s, CH₃), 0.78 (3 H, t, J = 7.0 Hz, OCH₂CH₃).

¹³C NMR (CDCl₃): δ = 196.7 (C=O), 143.9, 139.8, 133.6, 133.56 (4 Cα⾃), 128.6, 128.5, 127.7, 127.5 (8 CH₂, 100.1 (C-6a), 83.4 (C-3), 66.2 (6 H, s, CH₃), 57.1 (OCH₂CH₃), 54.7 (C-3a), 32.4 (C-4), 20.7 (CH₂), 15.0 (OCH₂CH₃).

FAB MS: m/z (%) = 391 (40, M – 45), 307 (30), 289 (18), 154 (100), 136 (77), 89 (12).
67.3 (C-3), 59.1 (OCH3CH3), 48.4 (C-4), 31.6 (C-5), 29.7 (COCH3), 21.1 (2C, 2 × CH3), 14.9 (OCH2CH3).

FAB MS: m/z (%) = 337 (68, M – 45), 239 (100), 119 (30), 91 (9). Anal. Calcd for C23H26O3S: C, 72.22; H, 6.85. Found: C, 72.08; H, 6.63.

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(9) (a) Actually, it is known that the Mn(OAc)3 consists of an oxygen-centered trinuclear complex, which is relatively stable in AcOH. However, when the oxidation was conducted in other solvents, such as EtOH, the trinuclear structure of Mn(III) might be deformed and the oxidizing ability weakened. (b) de Klein, W. J. In Organic Syntheses by Oxidation with Metal Compounds; Mijs, W. J.; de Jonge, C. R. H. I., Eds.; Plenum: New York, 1986, 261–314.


(14) The oxidation of 11m only with Mn(OAc)2 gave 21m in 60, 48, and 37% yield, respectively. Compare these with the yields described in Table 1, entries 15–17.
(15) The most stable conformation of 3,4-trans-pyrrolidinone 3a was calculated to be $-310.0$ kJ/mol by Spartan '06 based on the PM3 parameter. The calculated dihedral angle between H-3 and H-4 was 128.9°. On the other hand, the 3,4-cis 3a was $-293.1$ kJ/mol and the dihedral angle was 27.3°.