Conversion of Homoallylic Alcohols with Alkene Protection to the Corresponding Methyl Ketones

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In the course of a total synthesis of the potent cytotoxic agents tedanolide 1a and 13-deoxy-tedanolide 1b,2 a good method was needed to carry out two specific transformations, namely, a reversible protection of the alkene of the homoallylic alcohol system 2 and the conversion of the homoallylic alcohol or ether into the methyl ketone 3.

Accordingly, it was necessary to protect the alkene functionality in order to permit the application of a "non-aldol aldol" process,3 thereby avoiding certain problems associated with allylic epoxide rearrangements.4 For example, when the oxirane 4 was treated with a silyl triflate in the presence of base, the major product obtained was the ketone 6 arising from cleavage of the allylic oxirane C–O bond rather than the expected non-aldol aldol product 5, which would have been formed by cleavage of the tertiary oxirane C–O bond. To prevent this undesirable rearrangement (to give 6 instead of 5), the alkene had to be protected. Herein we describe our successful attempt at protecting the alkene of 2 coupled with selective oxidation, reductive ring opening, and final conversion to the methyl ketone 3.

Cyclization of either the homoallylic alcohols or the corresponding benzyl ethers 2a–f to the bromotetrahydrofurans 7a–f was carried out (Table 1) by treatment with N-bromosuccinimide (NBS) in dichloromethane to give only one diastereomer of the desired products.5,6 This diastereoselectivity can be explained by postulating that bromination proceeds via addition of the positive bromine to the bottom face of the alkene in conformation I with the hydrogen "inside" concomitant attack of the oxygen on the top face (with loss of a proton or benzyl cation)7 to give 7. The stereochemistry of the products was proven rigorously for compounds 7d and 7f by NOESY experiments (correlations shown below) and has been assigned by analogy for 7a–c.

Table 1. Formation of 3 from 2 via Intermediates 7, 8, and 9

<table>
<thead>
<tr>
<th>compd</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>yields (%)</th>
</tr>
</thead>
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<tr>
<td>a</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>60  93  86  67</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>86  82  87  66</td>
</tr>
<tr>
<td>c</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>48  82  76</td>
</tr>
<tr>
<td>d</td>
<td>CH₂OTBS</td>
<td>Me</td>
<td>Bn</td>
<td>64  88  70  52</td>
</tr>
<tr>
<td>e</td>
<td>CH₂OTBS</td>
<td>Me</td>
<td>H</td>
<td>86</td>
</tr>
</tbody>
</table>

(1) UCLA President’s Fellow, 1994–1998. Awardee of Excellence for First Year Graduate Study Award, 1995.
(6) For an example of this less common 5-endo cyclization, see: Mihailovic, M. Lj.; Marinovic, D. J. Org. Chem. 1983, 50, 5.
Having protected the alkenoate as a bromo ether, further transformations of the R1 group were possible. To regenerate the alkenoate and eventually to prepare the desired methyl ketone, we decided to oxidize the tetrahydrofurans 7 to the lactones 8. This was accomplished using RuCl3 and NaIO4 in the preferred mixed solvent system furans methyl ketone, we decided to oxidize the tetrahydrofurans to the alkene and eventually to prepare the desired lactones. Reductive ring opening was then effected with zinc dust in aqueous ethanol to give the alkenoic acids 9 in 70–87% yield. Simple reduction of the bromotetrahydrofurans 7 to regenerate the homoallylic alcohols was unsuccessful with zinc or a variety of other reducing agents, although it was cleanly carried out with tert-butyllithium. Finally, the acids 9, on treatment with lithium dimethycuprate, were converted to the methyl ketones via their crude acid chlorides (prepared by reaction with oxalyl chloride) to give 3 in 52–67% yield.

We have thus shown that bromomethylenation of homoallylic alcohols and ethers occurs diastereoselectively to give bromotetrahydrofurans (where the alkene functionality has been protected), which are cleanly oxidized to the lactones, reduced to the alkenoic acids, and converted into the desired methyl ketones. Further work on the “non-aldol aldol” process and the synthesis of the tedanolides will be reported in due course.

Experimental Section

General Methods. All reactions were carried out under argon with the exclusion of moisture. Reagents were purchased from commercial sources and used without further purification unless otherwise specified. The following solvents and reagents were distilled from the indicated agent under argon: tetrahydrofuran (THF) and diethyl ether from sodium benzophenone ketyl; dichloromethane, benzene, and toluene from calcium hydride; triethylamine from calcium hydride. Flash column chromatography was carried out in the indicated solvent system on 230–400 mesh silica gel. The proton nuclear magnetic resonance (1H NMR) spectra were recorded at 200 and 500 MHz, and the carbon nuclear magnetic resonance (13C NMR) spectra were recorded at 50 and 125 MHz. Spectra were taken in the indicated solvent at ambient temperature, and the chemical shifts are reported in parts per million relative to the solvent used. The infrared (IR) spectra were recorded on a Fourier transform IR spectrometer.

General Procedure for the Preparation of the 3-Pentenoic Acids, 9. Excess zinc dust was suspended in ethanol containing a small amount of water. The zinc suspension was treated with a solution of lactone 8 (0.4–1.0 mmol) in ethanol (4 mL). The mixture was refluxed for 5 h and cooled to room temperature. Insoluble particles were filtered through Celite. The filtrate was concentrated in vacuo and extracted with diethyl ether (2 × 20 mL). The organic phase was extracted with 10% Na2CO3 (2 × 20 mL), followed by acidification with cold concentrated HCl and subsequent extraction with diethyl ether (4 × 50 mL). The organic phases were washed with brine (30 mL), dried over MgSO4, and vacuum concentrated to give the 3-pentenoic acid 9.

1,2-Dimethyl-3-pentenoic acid, 9a. Zinc dust (3.14 g, 48 mmol) and lactone 8a (191 mg, 1.0 mmol) gave 110 mg (86%) of the known carboxylic acid 9a. The spectroscopic data for 9a matched that reported in the literature.

4-Methyl-2-phenyl-3-pentenoic Acid, 9b. Zinc dust (4.71 g, 72 mmol) and lactone 8b (380 mg, 1.50 mmol) gave 249 mg (87%) of carboxylic acid 9b. 1H NMR (CDCl3, 200 MHz) δ: 7.40 (5H, m), 5.53 (1H, dm, J = 9.4 Hz), 4.49 (1H, d, J = 9.4 Hz), 1.69 (3H, d, J = 1.1 Hz), 1.59 (3H, d, J = 1.3 Hz). 13C NMR (CDCl3, 50 MHz) δ: 179.16, 138.87, 135.71, 128.70, 127.90, 127.20, 121.39, 50.42, 25.86, 25.74. IR (neat): 3500–3100 (br), 2978, 2928, 2856, 1736, 1456, 1116 cm⁻¹.

4-Methyl-3-pentenoic Acid, 9c. Zinc dust (1.30 g, 19.8 mmol) and lactone 8c (80 mg, 0.414 mmol) gave 36 mg (76%) of 4-methyl-3-pentenoic acid 9c. 1H NMR (CDCl3, 200 MHz) δ: 7.37 (5H, m), 3.33 (1H, m), 1.59 (3H, d, J = 1.1 Hz), 1.19 (3H, t, J = 7.0 Hz), 0.94 (9H, s), 0.02 (6H, s). 13C NMR (CDCl3, 50 MHz) δ: 181.23, 137.27, 122.72, 67.96, 38.33, 25.89, 18.37, 17.63, 13.58 (two high-field carbons not recorded). IR (neat): 3450–3100 (br), 2968, 2924, 1708, 1414, 1302, 1221, 1155 cm⁻¹.

3E)-2,4-Dimethyl-5-[[((1,1-dimethylethyl)dimethylsilyl)oxy]-3-pentenoic Acid, 9d. Zinc dust (3.14 g, 48 mmol) and lactone 8d (300 mg, 0.89 mmol) gave 160 mg (70%) of carboxylic acid 9d. 1H NMR (CDCl3, 200 MHz) δ: 5.38 (1H, bs), 5.21 (1H, m, J = 7.1 Hz), 2.98 (2H, d, J = 7.2 Hz), 1.95 (3H, s), 1.56 (3H, q, J = 6.1 Hz). 13C NMR (CDCl3, 50 MHz) δ: 178.85, 136.12, 115.11, 33.53, 25.56, 25.24. IR (neat): 3450–3100 (br), 2968, 2924, 1708, 1414, 1302, 1221, 1155 cm⁻¹.

General Procedure for the Conversion of the Acid 9 into the 4-Hexen-2-one, 3. A solution of the acid 9 (0.5–1 mmol) in methylene chloride was treated with a 2 M oxalyl chloride solution in methylene chloride. After the mixture had stirred for 4 h at room temperature, it was concentrated under vacuum to produce the crude acid chloride, which was dissolved in THF and added at −78 °C to a THF solution of lithium dimethylcuprate, previously prepared by addition of 1 M methyllithium (2 equiv) to a suspension of copper(I) iodide (1 equiv) in THF at 0 °C and stirred at room temperature for 10 min. After the THF solution had stirred for 1 h, the reaction was quenched by the sequential addition of methanol and saturated NH4Cl at −78 °C. The organic phase was removed under vacuum. The remaining aqueous phase was extracted with diethyl ether, dried over MgSO4, and purified by flash column chromatography (silica gel, 50% diethyl ether:hexanes) to give the enone 3.

3,5-Dimethyl-4-hexen-2-one, 3a. The acid 9a (100 mg, 0.780 mmol) gave 66 mg (67%) of the known enone 3a. The spectroscopic data for 3a matched that reported in the literature.

5-Methyl-3-phenyl-4-hexen-2-one, 3b. The acid 9b (200 mg, 1.05 mmol) gave 130 mg (66%) of compound 3b. 1H NMR (CDCl3, 200 MHz) δ: 7.25 (5H, m), 5.62 (1H, dm, J = 9.4 Hz), 4.52 (1H, d, J = 9.4 Hz), 2.08 (3H, s), 1.76 (3H, d, J = 0.9 Hz), 1.69 (3H, d, J = 1.3 Hz). 13C NMR (CDCl3, 50 MHz) δ: 207.14, 139.26, 135.43, 128.85, 128.05, 127.01, 121.53, 58.82, 28.27, 25.89, 18.24.

IR (neat): 2972, 2914, 2860, 1716, 1610, 1493, 1354, 1155, 750, 700 cm⁻¹.

Notes

General Procedure for the Formation of the 3-Bromotetrahydrofurans. 7. The 3-ponent-1-ol 2 (1 equiv) was dissolved in anhydrous methylene chloride. N-Bromosuccinimide (NBS, 2 equiv) was added, and the mixture was refluxed in the dark for 8 h. The solvent was evaporated, pentane was added, and the suspension was filtered. The filtrate was concentrated under vacuum. It was flash column chromatographed (silica gel, 20% diethyl ether:hexanes) to yield the bromotetrahydrofuran 7.

trans-3-Bromo-2,2,4-trimethyltetrahydrofuran, 7a. 2,4-Dimethyl-3-penten-1-ol, 2a (400 mg, 3.50 mmol), gave 406 mg (60% of compound 7a. 3H NMR (CDCl3, 200 MHz) ð 3.95 (1H, app t, J = 8.5 Hz), 3.42 (1H, J, d = 8.7 Hz), 3.22 (3H, s), 2.25 (1H, m), 1.44 (6H, bs), 1.28 (3H, d, J = 10.3 Hz), 1.19 (3H, s), 1.18 (3H, s), 1.09 (3H, d, J = 6.6 Hz). 13C NMR (CDCl3, 50 MHz) ð 62.25, 25.73.

General Procedure for the Formation of the 4-Bromomethyltetrahydrofuran-

4. The product was extracted with methylene chloride. The combined organic phases were dried over MgSO4. After evaporation of the solvent, diethyl ether was added and the suspension was filtered through Celite. The solvent was removed under vacuum to produce a crystalline solid which, upon washing with cold pentane, yielded the bromoactones.

trans-4-Bromomethyl-3,5,5-trimethyltetrahydrofuran-2(3H)-one, 8a. 3-Bromo-2,2,4-trimethyltetrahydrofuran, 7a (130 mg, 0.67 mmol), yielded 120 mg (93%) of compound 8a. 3H NMR (CDCl3, 200 MHz) ð 3.76 (1H, d, J = 11.9 Hz), 2.80 (1H, dd, J = 11.9 Hz, 7.0 Hz), 1.61 (3H, s), 1.58 (3H, s). 13C NMR (CDCl3, 50 MHz) ð 162.20, 133.39, 129.03, 128.55, 128.44, 86.45, 57.06, 55.00, 26.10, 24.06. IR (neat): 2959, 2924, 2853, 1753, 1456, 1375, 1295, 1095, 734, 698 cm⁻¹.

4-Bromomethyl-5,5-dimethyltetrahydrofuran-2(3H)-one, 8b. 3-Bromo-2,2,4-4-tertbutyltetrahydrofuran, 7b (1.70 g, 6.66 mmol), yielded 1.38 (82%) of compound 8b. 3H NMR (CDCl3, 200 MHz) ð 7.30 (5H, m), 4.20 (1H, dd, J = 11.9 Hz), 4.01 (1H, d, J = 11.9 Hz), 1.61 (3H, s), 1.58 (3H, s). 13C NMR (CDCl3, 50 MHz) ð 162.20, 133.39, 129.03, 128.55, 128.44, 86.45, 57.06, 55.00, 26.10, 24.06. IR (neat): 2959, 2924, 2853, 1753, 1456, 1375, 1295, 1095, 734, 698 cm⁻¹.

Supporting Information Available: 1H and 13C NMR spectra of all new compounds and the NOESY data for compounds 7d and 7f (30 pages). This material is contained in libraries on microfiche, immediately follows this article in the ACS; see any current masthead page for ordering information.

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