Facile One-Pot Procedure for Et₃Al-Promoted Asymmetric Pinacol-Type Rearrangement

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Received 25 September 2002; revised 4 November 2002

Abstract: A facile procedure for the synthesis of enantiomerically pure α-substituted ketones is described. The pinacol-type 1,2-shift of sec-tert 1,2-diols could be effected by performing the following two processes in a one pot procedure, (1) regioselective methanesulfonylation, and (2) direct treatment of the resulting mesylate with Et₃Al. This procedure allowed 1,2-shift reactions of various groups, including vinyl, aryl, and heteroaromatic groups, giving enantio-merically pure ketones in high yields.

Key words: α-chiral ketone, diols, Lewis acids, rearrangements, triethylaluminum

Previously, we reported an enantiospecific access to α-chiral ketones via Et₃Al-promoted stereospecific pinacol-type 1,2-shift of 1,2-diols (Scheme 1).1

Scheme 1

Et₃Al is a particularly effective Lewis acid, with the mechanism proceeding through unstable intermediate A, activating the mesyloxy leaving group, and also serving as an acid scavenger. The salient features are, (1) the migration proceeds stereospecifically with inversion of the pre-existing sec-alcohol center, (2) among the two potential migrating groups, the one with higher migratory aptitude selectively undergoes 1,2-shift, without regard to the stereochemistry of the tert-alcohol due to the flexibility of the 7-membered chelate intermediate, and (3) the reaction conditions are mild enough to allow the preparation of labile ketones, such as β,γ-unsaturated ketones. This reaction has been successfully applied to enantioselective syntheses of several natural products, including an alarm pheromone of an ant species,2a eldanolide,2b and protomycinolide IV2c (Figure 1).

Prior to this work, a two-step protocol was employed as outlined in Scheme 1. The first step (1→2) was the methanesulfonylation of sec-tert 1,2-diol 1, which proceeded regioselectively under sulfene generating conditions (MsCl, Et₃N, CH₂Cl₂, 0 °C).3 After simple extractive workup to remove triethylamine hydrochloride, drying and evaporation, the crude mesylate 2 was dissolved in CH₂Cl₂ and treated with Et₃Al at –78 °C to effect the 1,2-shift, thereby obtaining chiral ketones 3 in an enantiospecific manner.

This protocol has been generally satisfactory as long as the intermediary mesylate 2 is tractable. We have experienced, however, some occasions where mesylate 2 was extremely unstable. Recognizing that such unstable mesylates share a structural feature that one of the potential migrating groups, R, had a high migratory aptitude, we reasoned that the instability could be due to the side reactions triggered by minute amounts of CH₃ SO₂ H, which may be formed by neighboring group participation of R. We recently encountered such a case in the attempted 1,2-shift of an N-methylindolyl group (Scheme 2). When diol 1a was sulfonlated by the above-stated procedure, the colorless crude mesylate 2a, obtained by extraction–evaporation, suddenly changed to a black oil. Although many by-products were present (TLC assay), we dared to treat the black material with Et₃Al. Not surprisingly, the yield of 3a was low, but fortunately the enantiomeric purity was preserved.

Since simple modification of the workup procedure failed to solve the problem, we endeavoured to carry out the mesylation–rearrangement sequence in one pot, despite the
presence of triethylamine hydrochloride, which may interfere with the Et₃Al-mediated 1,2-shift process. We report herein that the one-pot procedure indeed provides a nice solution to this issue.

As an initial feasibility study, we examined the one-pot conversion of diol 4 into ketone 6. Diol 4 was converted to mesyloxy alcohol 5 by treatment with CH₃SO₂Cl (1.05 equiv) and Et₃N (1.1 equiv) at 0 °C in CH₂Cl₂. After stirring for 10 min, when completion of the reaction was verified by silica-gel TLC, the mixture was cooled to –78 °C, and Et₃Al was added. It was found that the desired 1,2-shift was feasible, but the amount of Et₃Al was critical to the outcome as summarized in Table 1. When Et₃Al was used roughly stoichiometrically (1.1 equiv relative to the starting diol 4), the yield of 6 was only 24%. Methyl ketone 7 was obtained as a side product in 31% yield, and 28% yield of unreacted mesylate 5 remained. The yield of 6 increased to 70% when 2 equivalents of Et₃Al were used, although the reaction was still incomplete, and the same by-products were again obtained. In sharp contrast, an excellent result was attained when 3 equivalents of Et₃Al were used. The yield of 6 was 86%, and the enantiomeric purity was 99% ee.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Et₃Al (equiv)</th>
<th>6 (%)</th>
<th>7 (%)</th>
<th>5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1.1</td>
<td>24</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>2a</td>
<td>2.0</td>
<td>70</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3b</td>
<td>3.0</td>
<td>86</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* Reaction was carried out at –78 → 0 °C for 20 min.
* Reaction was carried out at –78 → –20 °C for 10 min.

### Biographical Sketches

**Tomoichi Shinohara** was born in 1965 in Ehime (Japan) and obtained his MSc degree in Chemistry in 1990 at the Ehime University of Japan. He worked for ten years (1990–1999) in the medicinal chemistry department at Otsuka Pharmaceutical Co., Ltd. (Tokushima, Japan), and then joined the Doctorate Program for Company Employees at Tokyo Institute of Technology under the direction of Professor K. Suzuki to study new methods for asymmetric synthesis. Recently, he restarted drug discovery research at Otsuka Pharmaceutical.

**Keisuke Suzuki** was born in 1954 at Chigasaki, Kanagawa Pref. Japan. He received BSc (1978), MSc (1980) and PhD (1983) degrees from the University of Tokyo under the guidance of Prof. Teruaki Mukaiyama. In 1983 he became a Research Associate (with the late Prof. Gen-ichi Tsuchihashi) at Keio University. He was promoted to Assistant Professor (1986), Associate Professor (1989), and then to Professor (1994) at Keio University. In 1996, he moved to his present position at Tokyo Institute of Technology. He spent a sabbatical as a visiting Professor at ETH, Zürich, Switzerland (with Prof. Dieter Seebach, 1990–1991). He received the Japan Chemical Society Award for Young Chemists, 1986, Takasago Award of the Synthetic Organic Chemical Society of Japan (1994), Japan IBM Award (1994), Teshima Award (1996), and Nagoya Silver Medal (1999). His research interests lies in the exploitation of new synthetic methods for selective synthesis of natural products.
Having identified the effective protocol for the one-pot conversion, we applied it to the aforementioned conversion of diol 1a into ketone 3a, and we were pleased to find that it was indeed effective. By applying exactly the same reaction conditions stated above for diol 1a, the indolyl group underwent smooth 1,2-shift, giving chiral ketone 3a in 85% yield in enantiomerically pure form as evidenced by the chiral HPLC analysis (Table 2, Entry 1).

The sequence proved to be effective also for other diols8 containing other various hetero-aromatics, and the corresponding chiral ketones were obtained in good yields with high enantiomeric purities (entries 2–5). For comparison, the yields obtained by the two-pot procedure are shown in parentheses in Table 2. Thus, the one-pot procedure enables the 1,2-shift reactions otherwise difficult due to instability of the intermediary mesylates, which is featured by much improved yields by the one-pot procedure in runs 2 and 3 in comparison with the two-pot procedure.

Furthermore, this one-pot procedure is not restricted to the case where intermediate mesylate was unstable, but generally applicable to the 1,2-rearrangement of various groups such as phenyl group (entry 6) and vinyl group (entries 7 and 8) to afford chiral ketones, which were previously prepared by the two-pot sequence.1

In conclusion, the pinacol-type 1,2-shift of 1,2-diols can be performed in one pot by consecutive treatment of diols with methanesulfonyl chloride and triethylamine at 0 °C followed by Et3Al at –78 °C. The protocol is especially effective in cases where the diol substrate has a potentially high migrating group and/or an acid labile substructure, such as entries 1 and 3 in Table 2.

All 1H NMR spectra were taken with JEOL Lambda 400 (400 MHz) spectrometer using tetramethylsilane as internal standard, and coupling constants were given in Hz. All 13C NMR were taken on the same instrument at 100 MHz, using the 13C signal of the deuterated solvent as internal reference for CDCl3 (δ = 77.0, central signal). The signals of the major component of a product mixture are marked with an asterisk (*). IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. Elemental analyses were carried out using a Perkin Elmer Series II 2400 CHNS/O Analyzer. Optical rotations were measured on a JASCO DIP-1000 instrument. HPLC analyses were performed with a JASCO PU-1580 using a JASCO CD-1595 detector (column, DAICEL CHIRALCEL OD-H, 25 × 0.46 cm; detection 254 nm light). Silica-gel chromatography was performed using Merck Silicagel 60.

### Table 2 One-Pot Conversion of Various Diols 1 to Ketones 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)a</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>3a</td>
<td>85 (39)</td>
<td>99b</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>3b</td>
<td>90 (76)</td>
<td>99b</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>3c</td>
<td>96 (21)</td>
<td>99b</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>3d</td>
<td>90 (89)</td>
<td>99b</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>3e</td>
<td>93 (90)</td>
<td>&gt;98c</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>3f</td>
<td>92 (86)</td>
<td>&gt;98d</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>3g</td>
<td>89 (75)</td>
<td>&gt;98d</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>3h</td>
<td>95 (75)</td>
<td>&gt;98d</td>
</tr>
</tbody>
</table>

a The numbers in parentheses refer to the yields in a two-pot protocol.

b Ee’s were determined by the chiral HPLC analysis (DAICEL CHIRALCEL OD-H, i-PrOH–n-hexane, 1:9).

c The ee was determined by 1H NMR analysis of the (R)-MTPA2 ester of the corresponding alcohol, which was prepared by treatment of 3e with DIBAL.

d Ee’s were determined by comparison with [α]D values and those reported previously,1a,b See experimental section.

### Scheme 3

Preparation of Diols 1 (Scheme 3): Typical Procedure

To a solution of 1-methylindole (0.60 mL, 4.7 mmol) and TMEDA (0.60 mL, 4.0 mmol) in anhyd Et2O (10 mL) was added BuLi (1.58 M in hexane, 2.5 mL, 4.0 mmol) at –78 °C. After stirring at 0 °C for 30 min, the reaction mixture was cooled to –78 °C, and (S)-2-(1-ethoxyethoxy)-5-phenylpentan-3-one1e (0.836 g, 3.33 mmol) was added. After stirring for 10 min, the reaction mixture was poured into water (20 mL), and the products were extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried (MgSO4), and solvents were removed in vacuo. The crude oil, thus obtained, was dissolved in EtOH (10 mL), to which was added pyridinium p-toluene sulfonate (167 mg, 0.666 mmol) at r.t. After stirring for 20 min, the reaction mixture was poured into water (20 mL), and products were extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried (MgSO4), and evaporated. The residue was purified by silica-gel column chromatography (hexane–EtOAc, 10:1 → 3:1) to give a...
53:47 diastereomeric mixture of diol 1a as a colorless oil (0.920 g, 89%).

(2S,3RS)-3-(1-Methyl-1H-indol-2-yl)-5-phenyl-2,3-pentanediol (1a)

IR (neat): 3412, 2942, 1466, 751 cm⁻¹.

1H NMR (CDCl₃): δ = 1.12 (1.59 H, d, J = 6.3 Hz), 1.24 (1.41 H, d, J = 6.3 Hz), 1.91 (0.53 H, d, J = 6.3 Hz), 2.16 (0.47 H, d, J = 2.7 Hz), 2.18–2.39 (2 H, m), 2.47 (0.53 H, s), 2.98 (0.47 H, s), 2.50–2.74 (2 H, m), 3.96 (1.59 H, s), 4.00 (1.41 H, s), 4.10 (0.53 H, quintet, J = 6.3 Hz), 4.37 (0.47 H, dq, J = 2.7, 6.3 Hz), 6.42 (0.53 H, s), 6.49 (0.47 H, s), 7.09–7.32 (8 H, m), 7.51–7.65 (1 H, m).

13C NMR (CDCl₃): δ = 15.7, 18.0, 30.2, 30.3, 32.3, 32.5, 37.3, 40.3*, 71.2, 73.1*, 77.8*, 78.7, 81.1, 101.1, 104.1*, 109.2*, 109.3, 119.8, 119.6*, 120.3*, 120.4, 121.4*, 121.8, 125.9*, 126.0, 126.9*, 127.1, 128.2*, 128.3, 128.5*, 138.4*, 138.8, 139.9, 140.2*, 141.7, 142.0*.

Anal. Calc'd for C₂₀H₂₂O₃ (312.43): C, 73.04; H, 6.45; S, 13.98*.

Found: C, 72.74; H, 6.59; S, 10.23.

1e Yield: 98%: colorless oil; dr 70:30.

IR (neat): 3430, 2930, 1496, 1452, 1085, 701 cm⁻¹.

1H NMR (CDCl₃): δ = 1.09 (0.9 H, d, J = 6.3 Hz), 1.22 (2.1 H, d, J = 6.3 Hz), 1.80 (0.3 H, d, J = 6.3 Hz), 1.87 (0.7 H, d, J = 3.8 Hz), 1.97–2.33 (2 H, m), 2.42 (0.7 H, dt, J = 4.6, 12.8 Hz), 2.54 (0.3 H, dr, J = 4.6, 12.8 Hz), 2.74 (1 H, dt, J = 4.6, 12.8 Hz), 2.87 (0.3 H, s), 2.91 (0.7 H, s), 3.90 (0.3 H, quintet, J = 6.3 Hz), 4.00 (0.7 H, dq, J = 3.8, 6.3 Hz), 6.92–7.20 (2 H, m), 7.12–7.32 (6 H, m).

13C NMR (CDCl₃): δ = 16.3*, 17.7, 29.8, 29.9*, 39.4*, 41.6, 74.2, 74.6*, 78.9*, 79.02, 123.7, 123.9*, 124.4, 127.7*, 125.8*, 127.0, 127.1*, 128.32*, 128.35, 128.4*, 142.1*, 146.9, 149.0*.

Anal. Calc'd for C₂₀H₂₂O₃ (326.37): C, 68.67; H, 6.91; S, 12.22.

Found: C, 68.94; H, 6.85; S, 12.26.

1f Yield: 92%; colorless oil; single diastereomer.

IR (neat): 3438, 2934, 1496, 1448, 1013, 700 cm⁻¹.

1H NMR (CDCl₃): δ = 1.19 (3 H, d, J = 6.3 Hz), 1.71 (1 H, ddd, J = 4.8, 12.1, 13.5 Hz), 1.94 (1 H, ddd, J = 5.3, 12.1, 13.5 Hz), 2.00 (1 H, br), 2.20 (1 H, br), 2.57 (1 H, ddd, J = 4.8, 13.5, 18.3 Hz), 2.70 (1 H, ddd, J = 5.3, 13.5, 18.3 Hz), 3.68 (1 H, q, J = 6.3 Hz), 5.36 (1 H, dd, J = 1.2, 10.6 Hz), 5.44 (1 H, dd, J = 1.2, 17.4 Hz), 5.89 (1 H, br, J = 10.6, 17.4 Hz), 7.14–7.31 (5 H, m).

13C NMR (CDCl₃): δ = 16.2, 17.9*, 28.9*, 38.4, 40.9*, 74.2*, 78.9*, 79.2, 125.7*, 125.8*, 126.0, 126.8*, 127.2, 128.2*, 128.3*, 142.4*, 142.4*, 142.4*.

Id Yield: 95%; colorless oil; single diastereomer.

IR (neat): 3442, 2953, 1244, 1030, 838 cm⁻¹.

1H NMR (CDCl₃): δ = 0.19 (5.67 H, s), 0.20 (3.33 H, s), 1.12 (1.89 H, d, J = 6.3 Hz), 1.18 (1.11 H, d, J = 6.3 Hz), 1.76–1.94 (2.37 H, m), 2.05–2.16 (1.26 H, m), and 2.42–2.74 (2.37 H, m), 3.74 (0.63 H, dq, J = 6.1, 6.3 Hz), 3.84 (0.37 H, dq, J = 3.6, 6.5 Hz), 5.62 (0.63 H, d, J = 1.7 Hz), 5.73 (0.37 H, s, J = 1.7 Hz), 5.66 (0.63 H, d, J = 1.7 Hz), 5.82 (0.37 H, s, J = 1.7 Hz), 7.11–7.30 (5 H, m).

13C NMR (CDCl₃): δ = 0.0*, 0.1, 15.5, 17.5*, 29.7*, 37.4, 41.1*, 72.1, 73.3*, 81.6*, 124.6*, 125.2*, 125.3, 126.1, 127.9*, 128.0*, 142.2*, 142.4, 155.4*, 156.1.

1h Yield: 85%; white solid; single diastereomer.

IR (neat): 3448, 2984, 2936, 1492, 1448, 995, 700 cm⁻¹.

Synthesis 2003, No. 1, 141–146 ISSN 0039-7881 © Thieme Stuttgart - New York
\[ 1^1 \text{H NMR (CDCl}_3\text{)}: \delta = 1.11 (3 \text{ H}, d, J = 6.3 \text{ Hz}), 1.83 (1 \text{ H}, d, J = 3.6 \text{ Hz}), 2.98 (1 \text{ H}, s), 3.81 (1 \text{ H}, q, J = 4.8 \text{ Hz}, 6.71-7.47 (8 \text{ H}, m), 7.61 (2 \text{ H}, dd, J = 1.5, 8.0 \text{ Hz}). \]
\[ 1^3 \text{C NMR (CDCl}_3\text{)}: \delta = 16.6, 71.6, 79.9, 125.5, 126.2, 126.8, 127.3, 128.1, 128.6, 145.6 (2 \text{ C}). \]

**(S)-4-(1-Methyl-3-indol-2-yl)-1-phenyl-3-pentanone (3a)**

To a solution of diol 1a (100 mg, 0.323 mmol) in anhyd CH\(_2\)Cl\(_2\) (2.0 mL) was added Et\(_3\)N (50 \( \mu \text{L}, 0.36 \text{ mmol}) and MsCl (26 \( \mu \text{L}, 0.34 \text{ mmol}) at 0 \text{°C} \text{ for 10 min.} \text{ The completion of the reaction was verified by silica-gel TLC (EtOAc–hexane, 1:1, Rf 0.46).} \text{ The reaction was cooled} \text{ to –78 °C,} \text{ and Et}_3\text{Al was added (0.93 mmol). After 10 min,} \text{ the reaction mixture was poured into aq KHSO}_4\text{,} \text{ and the products were extracted with EtOAc (3 × 20 mL).} \text{ The combined extracts were washed with water (20 mL) and brine (20 mL), dried (MgSO}_4\text{), and concentrated.} \text{ The residue was purified by silica-gel column chromatography (hexane–EtOAc, 20:1) afforded 3a as a colorless oil (80.0 mg, 85%).} \text{ The ee was determined to be 99% by chiral HPLC analysis [i-PrOH–hexane, 1.9 at 0.7 mL/min;} t\textsubscript{R} \text{(the major enantiomer} = 34.2 \text{ min, } t\textsubscript{R} \text{(the minor enantiomer} = 17.1 \text{ min; [} \text{ee} = 99%. \text{ IR (neat):} 2978, 1716, 1453, 1103, 747 \text{ cm}^{-1}. \text{ Yield:} 90\%; \text{ colorless oil; [} \lambda\text{max}^{24} = 465 \text{ (c 0.67, CHCl}_3\text{).} \text{ (continued...)} \]
$^{13}$C NMR (CDCl$_3$): $\delta$ = 17.3, 29.9, 42.5, 53.1, 126.0, 127.1, 127.8, 128.2, 128.9, 128.3, 128.4, 128.9, 140.4, 141.0, 209.8.

3g
Yield: 89%; colorless oil; $[\alpha]_D^{26}$+140 (c 1.16, CHCl$_3$) [lit. $^{1a}$ $[\alpha]_D^{27}$+135 (c 0.34, CHCl$_3$)].

IR (neat): 2976, 1716, 1453, 945, 921, 700 cm$^{-1}$.

$^1$H NMR (CDCl$_3$): $\delta$ = 1.15 (3 H, d, $J$ = 7.0 Hz), 2.67–2.93 (4 H, m), 3.17 (1 H, dq, $J$ = 8.2, 7.0 Hz), 5.11 (1 H, d, $J$ = 10.0 Hz), 5.13 (1 H, d, $J$ = 17.2 Hz), 7.13–7.22 (3 H, m), 7.23–7.32 (2 H, m).

$^{13}$C NMR (CDCl$_3$): $\delta$ = 15.6, 29.7, 42.3, 51.4, 116.9, 126.0, 128.3, 128.4, 137.3, 141.1, 210.4.

3h
Yield: 95%; colorless oil; $[\alpha]_D^{26}$ +131 (c 1.17, CHCl$_3$) [lit. $^{1b}$ $[\alpha]_D^{25}$ +131 (c 1.2, CHCl$_3$)].

IR (neat): 2955, 1712, 1455, 1249, 839, 699 cm$^{-1}$.

$^1$H NMR (CDCl$_3$): $\delta$ = 0.00 (9 H, s), 1.01 (3 H, d, $J$ = 6.8 Hz), 2.50 (1 H, ddd, $J$ = 6.5, 8.2, 15.2 Hz), 2.58–2.84 (3 H, m), 3.17 (1 H, q, $J$ = 6.8 Hz), 5.35 (1 H, d, $J$ = 1.4 Hz), 5.42 (1 H, d, $J$ = 1.4 Hz), 7.01–7.09 (3 H, m), 7.11–7.19 (2 H, m).

$^{13}$C NMR (CDCl$_3$): $\delta$ = −1.4, 17.0, 30.1, 42.7, 51.4, 125.9, 126.9, 128.3, 128.4, 141.2, 151.2, 210.1.

6
Yield: 85%; colorless oil; $[\alpha]_D^{19}$+196 (c 1.10, CHCl$_3$) [lit. $^{1a}$ $[\alpha]_D^{22}$+200 (c 1.1, CHCl$_3$)].

IR (neat): 2975, 1682, 1597, 1448, 1220, 952, 758, 689 cm$^{-1}$.

$^1$H NMR (CDCl$_3$): $\delta$ = 1.53 (3 H, d, $J$ = 6.8 Hz), 4.68 (1 H, q, $J$ = 6.8 Hz), 7.15–7.52 (8 H, m), 7.95 (2 H, d, $J$ = 8.2 Hz).

$^{13}$C NMR (CDCl$_3$): $\delta$ = 19.5, 47.9, 126.9, 127.7, 128.5, 128.7, 129.0, 132.7, 136.4, 141.4, 200.3.

References
(5) Diol 4$^a$ was prepared by the reaction of (S)-ethyl lactate with phenyllithium at −78 °C as shown in Scheme 4.

\[ \text{CO}_2\text{Et} \rightarrow \text{PhLi} \rightarrow \text{OH} \text{Ph} \]
\[ \text{HO} \text{Ph} \]
\[ \text{THF} \text{–78 °C, 5 min} \]

(S)-ethyl lactate

Scheme 4

(6) The ee was determined by comparison with the $[\alpha]_D$ value reported in ref 1a.
(7) Diol 1a was readily prepared by introduction of 1-methyl-2-indolyl group to chiral ketone 8, followed by removal of the ethoxyethyl group as shown in Scheme 3.
(8) Diols 1b–h were also prepared in a similar manner shown in Scheme 3.