Novel Base-Induced [1,2]-Acyl Shift of Allylic Esters of Cyclopropanecarboxylic Acids

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Introduction and Background

The cylindramides are marine natural products containing a tetramic acid lactam and an interesting bicyclo[3.3.0] ring system.1 Cylindramide 1 has shown strong cytotoxicity against cancer cell lines (IC50 of 0.8 mg/mL against B16 melanoma cells) while several other natural products with structures similar to that of cylindramide have interesting biological properties.2-5 Our synthetic studies on the cylindramides focused on the use of a novel, tandem radical rearrangement to synthesize the bicyclo[3.3.0]octane ring system of the natural product.

Previous work on a model system had validated the radical rearrangement that we planned to use in preparing the bicyclic core.6,7 Thus, treatment of the ester (R-O)2 with the thiolate radical generated from dibutyl disulfide led to the tricyclic compounds (±)-3a and (±)-3b (Scheme 1). The major product of the cyclization, however, was compound (±)-3a, which contained the undesired cis-anti-cis ring geometry, rather than the compound (±)-3b with the desired cis-syn-cis ring geometry.

Nevertheless, we reasoned that a sterically large, removable substituent α to the ester carbonyl could conceivably direct the cyclization to give the cis-syn-cis ring geometry as in the tricyclic compound 5. We therefore decided to prepare and study the model system 4, in which a silyl group α to the ester carbonyl might encourage the formation of the desired ring geometry. We proposed that 4 could be easily prepared from 2 as shown in Scheme 2 by silylation of the ester enolate since silylations of analogous cyclopropane carboxylates on carbon had been reported earlier by Larson.8

Results and Discussion

Treatment of the ester (±)-2 with base followed by silylating agents (trimethylsilyl chloride, methyldiphenylsilyl chloride) led to complex mixtures of products. To determine whether we were, in fact, generating the enolate, we attempted to trap the enolate with more reactive electrophiles. Surprisingly, the only products cleanly isolated from these reactions were the rearranged products (±)-6, in which the ester moiety had rearranged into an α-hydroxyketone (Table 1). In all cases, the products 6 were obtained as a 1:1 mixture of diastereomers.

The structures of the products 6 suggested a [1,2]-shift of the acyl group (Scheme 3) which could occur from the allylic anion A by a normal [1,2]-Wittig rearrangement,9 e.g., via the radical intermediate B, to give the alkoxide C. However, it is also possible that an intramolecular nucleophilic addition took place wherein the allylic anion A attacked the ester carbonyl to give the oxiranol anion D, which then underwent ring opening by breaking the C–O bond to give the alkoxide C. Deprotonation of the alkoxide C would then give the dianion E, an enediolate, which could react with electrophiles to give the observed products 6.

Similar rearrangements have been reported in the literature.\textsuperscript{10} For example, benzyl benzoate (7a) on treatment with LiTMP afforded benzoin benzoate (8a); benzylic pivalate (7b) when treated with LDA furnished the \( R \)-hydroxyketone (8b); and alkyl \( R \)-acyloxyacetates (7c) gave the \( R \)-hydroxy-\( \beta \)-keto esters (8c) on treatment with LDA (Scheme 4). In the first two cases, there is no possibility of forming the normal anion \( R \) to the ester since there are no \( R \)-protons present, while in the last case the difference in acidity greatly favors the anion \( R \) to both the ester and the acyloxy group. In our case destabilization of the anion of the cyclopropanecarboxylate, due to I strain, presumably causes the reaction to occur via the 1,2-shift pathway rather than via simple deprotonation of the ester. We have no evidence to support either of the two mechanistic possibilities although the oxiranol anion intermediate has been suggested to be involved in similar rearrangements\textsuperscript{10c} and thus may be the most likely intermediate in the present case.

Since the compounds (6) were isolated from complex product mixtures, we reasoned that we could better study the reaction mechanism by removing the cyclopentene olefin, thus reducing the number of diastereomerically different products and facilitating their identification (Scheme 5). We therefore prepared the saturated acid (10) by reduction of the unsaturated acid (9) followed by a Mitsunobu reaction\textsuperscript{11} to give ester (11) and examined its reactions with base and methyl iodide. Unfortunately,

\begin{table}[h]
\centering
\caption{Table 1}
\begin{tabular}{|l|l|l|l|}
\hline
base & temp, °C & \( E^+ \) & solvent & modifications & products \\
\hline
LDA & -78 to rt to -78 & Mel & THF & 6a, 25% recovered 2 \\
NaH & -78 to 0 to -78 & rt & MeI & 6b, 28% recovered 2 \\
LDA & -78 to 0 to -78 & allyl bromide & THF & 6c, 23% \\
LDA & -78 to 0 to -78 & H2O & THF & 6c, 18% \\
LDA & 0 °C & H2O & t-BuLi & 6c, 46% \\
LDA & 0 °C & H2O & THF & THF/dioxane \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Table 2}
\begin{tabular}{|l|l|l|l|}
\hline
base & temperature, °C & modifications & products \\
\hline
LDA & -78 to 0 to 78 & LiCl (4 equiv) & 12, 22% \\
LDA & -78 to 78 & 18-crown-6 & recovered 11 \\
NaH & -78 °C to rt & 18-crown-6 & decomposition \\
KH & -78 °C to rt & 18-crown-6 & recovered 11 \\
KHMDS & -78 to 0 to -78 & 18-crown-6 & recovered 11 \\
\hline
\end{tabular}
\end{table}

\begin{scheme}[h]
\caption{Scheme 3}
\end{scheme}

\begin{scheme}[h]
\caption{Scheme 4}
\end{scheme}

\begin{scheme}[h]
\caption{Scheme 5}
\end{scheme}

\addcontentsline{toc}{section}{Notes}

\textsuperscript{(11)} Mitsunobu, O. Synthesis 1981, 1.
the reactions of the ester 11 gave product mixtures that were similar in complexity to those obtained from the ester 2. The reactions of the esters 2 and 11 do, however, reveal the important role of the base. Sodium hydride did not effect the expected rearrangement of 11, even in the presence of 18-crown-6. Similarly, potassium hexamethyldisilazane did not cause the rearrangement. These studies suggest that the strength of the base may be important in determining whether the reaction does indeed occur.

To ascertain whether the bicyclo[3.1.0] cores of the esters 2 and 11 played a role in the rearrangement, we next prepared the less elaborate ester 13 (Scheme 6). As anticipated, the ester 13 also participated in this novel [1,2] shift, although the rearranged product 14 was isolated only in low yield.

In conclusion, we have discovered a novel base-induced rearrangement of allicyl esters of cyclopropane carboxylates. Treatment of these esters with bases of sufficient strength causes the formation of the allylic anion (homoenolate) which undergoes a [1,2]-acyl shift, leading to the formation of the enolate of the corresponding α-hydroxyketones, which on addition of electrophiles affords the trapped products in fair yield.

### Experimental Section

**General.** 1H NMR spectra were recorded at 360.134 MHz, 400.130 MHz, or 500.130 MHz and are so indicated. 13C NMR were recorded at 90.556, 100.613, or 125.773 MHz and are so indicated. 1H NMR and 13C NMR data are reported in parts per million (δ) downfield from tetramethylsilane. Infrared spectra were recorded on an FTIR as a film. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F254 0.2 mm plates. Flash chromatography was carried out using ICN Bio-resources silica gel 60 (230–400 mesh). Solvent systems are reported as volume percent mixtures. All inorganic solutions are reported as volume percent mixtures. All inorganic solutions are reported as volume percent mixtures. All inorganic solutions are reported as volume percent mixtures. All inorganic solutions are reported as volume percent mixtures.

**Notes**


washed with brine, dried (MgSO4), filtered, and concentrated to an oil. Flash chromatography over silica gel (15% ethyl acetate/hexanes) provided the hydroxy ketone, 6c, as a colorless oil (23.5 mg, 23%). As an inseparable 1:1 mixture of diastereomers. 1H NMR (360 MHz, CDCl3): δ: 5.96 (m, 2H), 5.62 (m, 2H), 5.02 (m, 2H), 4.95 (m, 2H), 3.78 (s, 1H), 3.77 (s, 1H), 2.71 (m, 2H), 2.55 (m, 2H), 2.50 – 2.25 (m, 4H), 1.84 (s, 6H), 1.81 (s, 6H), 1.23 (s, 1H), 1.22 (s, 1H). 13C NMR (CDCl3, 90 MHz) δ: 209.0, 208.8, 139.9, 139.8, 132.3, 132.2, 131.2, 131.1, 121.4, 121.1, 74.4 (2 C's), 38.5, 38.2, 36.6, 36.5, 35.5, 35.2, 30.2, 29.9, 25.9 (2 C's), 18.6, 18.5. IR (neat) 3457, 3063, 2973, 2913, 1690, 1618, 1445 cm⁻¹.

(--)-[3-Methyl-2-butenyl] 1α, 5α, 6α-Bicyclo[3.1.0]hexane-6-carboxylic acid, 10. The carboxylic acid 9 (2.95 g, 24 mmol) was weighed into a 50 mL flask. The flask was flushed with argon and benzene (25 mL) was added. Palladium on carbon (5%, 0.5 g) was added to the reaction, and the flask was flushed with hydrogen from a balloon. The balloon was replaced as it lost pressure, and the reaction was stirred at room temperature until 1H NMR of aliquots taken from the reaction showed that the reaction was complete. The reaction was filtered through Celite, and then 100 mL of a saturated sodium bicarbonate solution was added. The mixture was shaken in a separatory funnel, and the organic layer was discarded. The aqueous phase was acidified to pH 1 with hydrochloric acid, and then 3 mL of a saturated sodium bicarbonate solution, dried (MgSO4), filtered, and concentrated to an oil. Flash chromatography over silica gel provided the hydroxy ketone, 10 as a colorless oil (23 mg, 22%). 1H NMR (400 MHz, CDCl3) δ: 7.25 (s, 6H), 1.23 (s, 1H), 1.22 (s, 1H). 13C NMR (CDCl3, 90 MHz) δ: 5.06 (d, J = 11.5 Hz, 1H), 1.75 (s, 3H), 1.59 (s, 3H), 1.42 (s, 3H), 1.30 (m, 5H), 1.75 (s, 3H), 1.55 (s, 3H), 1.42 (s, 3H), 1.30 (m, 5H). 11C NMR (CDCl3, 90 MHz) δ: 174.9, 138.8, 118.7, 61.4, 25.7, 17.9, 12.8, 8.3. IR (neat) 3017, 2975, 2936, 2721, 21.0. 1R (neat) 3050, 2985, 2867, 2760, 1690. 1445 cm⁻¹.

3-Methyl-2-buten-1-yl Cyclopropanecarboxylate, 13. Into a 50 mL flask under argon was added dichloromethane (25 mL). The flask was cooled to 0 °C, and 3-Methyl-2-buten-1-ol (1.75 mL, 17.4 mmol) was added, followed by triethylamine (5 mL, 35 mmol). Cyclopropanecarbonyl chloride (1.6 mL, 17.4 mmol) was added dropwise, followed by DMAP (0.1 g, 0.82 mmol). The reaction was warmed to room temperature, giving a solution thick with white precipitate. The solution was washed with 10% potassium dihydrogen phosphate solution, until the pH of the aqueous layer was below 5. The organic solution was washed with saturated sodium bicarbonate solution, dried (MgSO4), filtered, and concentrated briefly by rotary evaporation. Kugelrohr distillation of the resulting oil provided the desired ester 13 as a colorless oil (2.47 g, 92%). 1H NMR (360 MHz, CDCl3) δ: 5.35 (br t, J = 7.2 Hz, 1H), 4.56 (dd, J = 7.2 Hz, 2H), 1.75 (s, 3H), 1.70 (s, 3H), 1.60 (br t, J = 11.5, 7.9 Hz, 1H), 0.99 (dd, J = 7.9, 3.7 Hz, 1H), 0.83 (dd, J = 11.5, 7.9 Hz, 1H), 0.83 (dd, J = 11.5, 7.9 Hz, 1H). 13C NMR (CDCl3, 75 MHz) δ: 174.9, 138.8, 118.7, 61.4, 25.7, 17.9, 12.8, 8.3. IR (neat) 3017, 2975, 2936, 2721, 21.0. 1R (neat) 3050, 2985, 2867, 2760, 1690. 1445 cm⁻¹.

1-Cyclopropyl-2-hydroxy-4-methyl-3-penten-1-one, 14. The allylic ester 13 (101 mg, 0.65 mmol) was weighed into an oven-dried 10 mL flask. The flask was flushed with argon, and THF (4 mL) was added. The flask was cooled to −78 °C, and a 3.8 mL of a freshly prepared 0.5 M LDA solution was added (0.98 mL disopropylamine + 2 mL THF, −78 °C). 1-Chloro-2-methyl-1-pentyne (0.5 mL, 3.6 mmol) was added, followed by 2-Methyl-2-buten-1-ol (1.75 mL, 17.4 mmol) was added, followed by triethylamine (5 mL, 35 mmol). Cyclopropanecarbonyl chloride (1.6 mL, 17.4 mmol) was added dropwise, followed by DMAP (0.1 g, 0.82 mmol). The reaction was warmed to room temperature, giving a solution thick with white precipitate. The solution was washed with 10% potassium dihydrogen phosphate solution, until the pH of the aqueous layer was below 5. The organic solution was washed with saturated sodium bicarbonate solution, dried (MgSO4), filtered, and concentrated briefly by rotary evaporation. Kugelrohr distillation of the resulting oil provided the desired ester 13 as a colorless oil (2.34 g, 92%). 1H NMR (360 MHz, CDCl3) δ: 5.35 (br t, J = 7.2 Hz, 1H), 4.56 (dd, J = 7.2 Hz, 2H), 1.75 (s, 3H), 1.70 (s, 3H), 1.60 (br t, J = 11.5, 7.9 Hz, 1H), 0.99 (dd, J = 7.9, 3.7 Hz, 1H), 0.83 (dd, J = 11.5, 7.9 Hz, 1H), 0.83 (dd, J = 11.5, 7.9 Hz, 1H). 13C NMR (CDCl3, 75 MHz) δ: 174.9, 138.8, 118.7, 61.4, 25.7, 17.9, 12.8, 8.3. IR (neat) 3017, 2975, 2936, 2721, 21.0. 1R (neat) 3050, 2985, 2867, 2760, 1690. 1445 cm⁻¹.

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Supporting Information Available: Proton NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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