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Orthoester Condensation/C-O Insertion Reaction Sequence for the Preparation of Tetrahydrofurans

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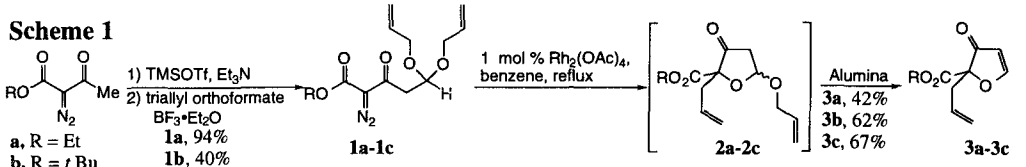
Abstract: This paper describes a general procedure for the efficient preparation of highly substituted tetrahydrofurans. The condensation of α-diazo-β-ketoester-derived enolates with orthoesters yields diazoacetals **1a-1d**. These compounds undergo formal C-O insertion reactions in the presence of $Rh_2(OAc)_4$ to afford tetrahydrofurylacetals **2a-2c**. Similar insertion reactions of diazoacetals **5a-5d** yield bicyclic acetals **6a-6d**, which possess cores similar to those of the zaragozic acids.

We recently reported an aldol-insertion reaction sequence for the efficient synthesis of tetrahydrofurans.[1] We now wish to report a related orthoester condensation/C-O insertion reaction sequence that allows the preparation of more highly substituted tetrahydrofuran ring systems (Scheme 1).

Scheme 1



We first developed a Lewis acid-mediated condensation of orthoesters with the silyl enol ethers of α-diazo-β-ketoesters to yield the allylic acetals **1a-1c** (Scheme 1).[2,3] Such condensations proceeded in high yields in the presence of $BF_3•Et_2O$ as the Lewis acid. Use of more powerful Lewis acids, such as $TiCl_4$, did promote the desired condensation, but also caused quantitative elimination of these products to the α,β-unsaturated ketones.

Allylic acetals **1a-1c** underwent C-O insertion reactions in the presence of $Rh_2(OAc)_4$, presumably through metal carbenoid and oxonium ylide intermediates, to give substituted tetrahydrofurans **2a-2c** as diastereomeric mixtures in high yields.[4] Copper(I) species such as CuOTf also catalyzed the insertion reactions, but in slightly lower yields. The instability of **2a-2c** to liquid or gas chromatography made purification and exact determination of diastereomeric excess difficult. Therefore, we treated **2a-2c** with alumina to afford the eliminated products, **3a-3c**, in moderate yields.

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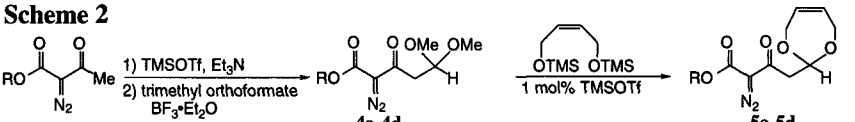
We next prepared and rearranged cyclic allylic acetals **5a-5d**. We synthesized these compounds by exchange reactions with dimethyl acetals **4a-4d** (Scheme 2).[5] Acetals **4a-4d** were in turn prepared by the same method used for the synthesis of **1a-1c**.

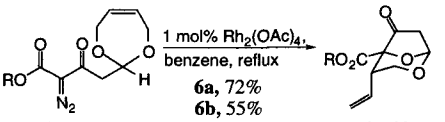
Scheme 2



a, R = Me — **4a**, 88% — **5a**, 83%
b, R = Et — **4b**, 75% — **5b**, 73%
c, R = Ph — **4c**, 64% — **5c**, 82%
d, R =2,4-dimethyl -3-pentyl — **4d**, 85% — **5d**, 90%

The insertion reactions of **5a-5d** were not as high yielding as those of **1a-1d**, but the products, **6a-6d**, were formed with high diastereoselectivity and were not prone to elimination (Scheme 3). The bicyclic cores of **6a-6d** are similar to the core of the zaragozic acids,[6] and also resemble the cores of compounds prepared by Zercher et al. by a related 1,2-C-O insertion reaction.[7] In contrast to Zercher's results with the 1,2-insertions, copper catalysts did not effectively catalyze the corresponding 2,3-insertions of **5a-5d**.

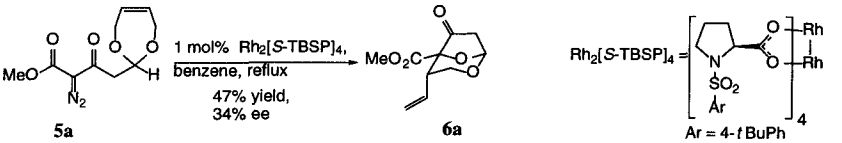
Scheme 3



5a-5d → **6a**, 72%; **6b**, 55%; **6c**, 48%; **6d**, 27% → **6a-6d**

We last examined the rearrangements of allylic acetals **1a-1c** and **5a-5d** catalyzed by chiral Rh(II) compounds.[8] The allylic acetals are achiral, yet rearrange to chiral compounds. We found no enantioselectivity in the rearrangements of **1a-1c** with a number of chiral catalysts.[9] However, compounds **5a-5d** rearrange to **6a-6d** with low enantioselection.[10] The combination of substrate **5a** with Davies' catalyst, $Rh_2[S\text{-TBSP}]_4$, afforded the highest induction (Scheme 4).[11]

Scheme 4



5a → **6a**

In summary, we have developed an efficient, two step method for the preparation of highly substituted tetrahydrofurans. We are currently attempting to convert compounds **6a-6d** into the zaragozic acid core. We are also attempting to improve the enantioselectivity of the C-O insertion reaction by using new catalysts and substrates.

General Procedure for the Synthesis of 1a-1c. To a solution of 0.500 g (3.2 mmol) ethyl 2-diazo-3-oxobutanoate in 8 mL of CH_2Cl_2 at -78 °C was added 0.83 mL (1.0 g, 4.6 mmol) TMSOTf and (0.58 g, 5.8 mmol) 0.81 mL Et_3N. This solution was then maintained at -78 °C for 30 min. In a separate flask, 0.85 g (4.6 mmol) triallylorthoformate[12] was added to 0.97 mL (1.1 g, 7.7 mmol) of BF_3•OEt_3 in 10 mL of CH_2Cl_2 at -78 °C. This heterogeneous mixture was maintained at -78 °C for 30 min, after which time the silyl enol

ether mixture from above was added dropwise. The combined reaction mixture was kept at -78 °C for 3.5 h, and then quenched by the addition of 10 mL pH7 buffer solution and warmed to room temperature. The organic phase was separated, washed with saturated aqueous $NaHCO_3$ (1 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo. The product was purified by flash chromatography (5% EtOAc in hexanes) to yield 0.85 g (94%) of **1a**: ^1H NMR ($CDCl_3$, 360 MHz) δ 1.30 (t, *J* = 7.1 Hz, 3 H), 3.25 (d, *J* = 5.7 Hz, 2 H), 4.12 (m, 4 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 5.10-5.30 (m, 5 H), 5.90 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ14.3, 44.3, 61.5, 67.0, 98.5, 116.9, 134.3, 161.1, 188.7; IR (Neat) 2134, 1717, 1649 cm^{-1}; HRMS(FAB) Cacld. for $C_{13}H_{19}N_2O_5$ (MH^+): 283.1294. Found: 283.1294.

General Procedure for the C-O Insertion Reactions of 1 to Form 3. To a suspension of 0.0050 g (0.0039 mmol) $Rh_2(OAc)_4$ in 2 mL refluxing benzene was added 0.110 g (0.39 mmol) **1a** in 3 mL benzene over 15 min. After an additional 15 min at relux, the mixture was cooled to room temperature and concentrated in vacuo. Chromatography on neutral alumina (5-10% EtOAc in hexanes) yielded 0.032 g (42%) of **3a**: ^1H NMR ($CDCl_3$, 360 MHz) δ 1.24 (t, *J* = 7.1 Hz, 3 H), 2.70 (dd, *J* = 14.5, 6.8 Hz, 1 H), 2.92 (dd, *J* = 14.5, 7.4 Hz, 1 H), 4.22 (m, 2 H), 5.15 (m, 2 H), 5.63 (m, 2 H), 8.30 (d, *J* = 2.6 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.0, 29.6, 62.7, 89.8, 106.0, 120.7, 129.3, 164.3, 178.2, 198.4; IR (Neat) 1747, 1709 cm^{-1}; HRMS (FAB) Calcd. for $C_{10}H_{13}O_4$ (MH^+): 197.0814. Found: 197.0809.

General Procedure for Acetal-Exchange Reactions of 4 to Form 5. To a mixture of 0.445 g (2.06 mmol) of **4a** (prepared by the same procedure used to prepare **2**) and 0.574 g (2.47 mmol) *cis*-1,4-bis(trimethylsiloxy)-2-butene in 4 mL CH_2Cl_2 was added 0.040 mL (0.046 g, 0.21 mmol) TMSOTf. After 30 min, the reaction mixture was warmed to -15 °C and maintained at this temperature for 20 h. The reaction was then quenched with 2 mL of pyridine, followed by 4 mL saturated aqueous $NaHCO_3$. The mixture was warmed to room temperature and the organic layer was separated, washed with 1 M aqueous $NaHSO_4$ (1 × 5 mL), dried over Na_2SO_4, and concentrated in vacuo. Chromatography over silica gel (5% EtOAc in hexanes) to yield 0.4080 g (83%) of **5a**: ^1H NMR ($CDCl_3$, 360 MHz) δ 3.25 (d, *J* = 5.7 Hz, 2 H), 3.81 (s, 3 H), 4.15 (d, *J* =14.3 Hz, 2 H), 4.37 (d, *J* =14.3 Hz, 2 H), 5.29 (t, *J* = 5.7 Hz, 1 H), 5.67 (m, 2 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 44.1, 52.3, 65.7, 100.7, 129.4, 161.5, 188.6; IR (Neat) 2139, 1721, 1650 cm^{-1}; Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.4; N, 11.6. Found: C, 49.93; H, 5.06; N, 11.58.

General Procedure for the Synthesis of C-O Insertion Reactions of 5 to Form 6. To a suspension of 0.0035 g (0.0027 mmol) $Rh_2(OAc)_4$ in 2 mL refluxing benzene was added 0.0650 g (0.27 mmol) **5a** in 2 mL benzene over 15 min. After an additional 15 min at relux, the mixture was cooled to room temperature and concentrated in vacuo. Chromatography on silica gel (5% EtOAc in hexanes) yielded 0.0410 g (72%) of **6a**: ^1H NMR ($CDCl_3$, 360 MHz) δ 2.67 (d, *J* =18.4 Hz, 1 H), 2.78 (dd, *J* = 8.76, 3.8 Hz, 1 H), 2.88 (dd, *J* =18.4, 5.4 Hz, 1 H), 3.70 (s, 3 H), 3.85 (d, *J* =12.7 Hz, 1 H), 4.17 (dd, *J* =12.7, 3.6 Hz 1 H), 5.26 (m, 2 H), 5.93 (d, *J* = 5.4 Hz, 1 H), 6.20 (ddd, *J* =17.2, 8.7, 8.4 Hz, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 41.1, 45.0, 53.0, 63.5, 85.2, 98.0, 119.7, 136.9, 164.9, 205.4; IR (Neat) 1770, 1739 cm^{-1}; Anal. Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.31; H, 5.73.

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