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New Chiral Building Blocks from Tetrabromocyclopropene and Furan

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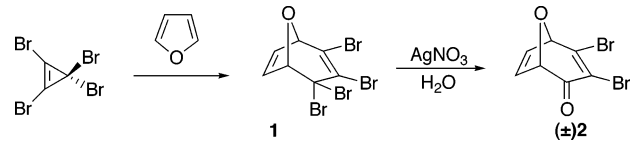
Abstract: The cyclocondensation of tetrabromocyclopropene and furan leads directly to a halogenated oxabicyclo[3.2.1]-octadiene derivative. Over the past several years, we have utilized these compounds as intermediates for natural product synthesis. Herein, we describe the preparation of nonracemic dibromoenone building blocks from the racemic cycloadduct. Conversion of the adduct to a mixture of tartrate-derived ketals followed by separation of the diastereomers and hydrolysis allows for the formation of novel chiral synthons with either absolute configuration.

Over the past several years, we have been interested in the utilization of the cycloadduct derived from furan and tetrabromocyclopropene[1] as a complementary synthon to those prepared through oxyallyl cation/furan cycloadditions.[2] This reaction produces a highly functionalized oxabicyclo[3.2.1]octadiene derivative **1** through an exo-selective Diels−Alder reaction and subsequent rearrangement.[3] Previously, we described[4] the conversion of the tetrabromo derivative **1** to the dibromoenone **2** through a silver-promoted hydrolysis (Scheme 1).

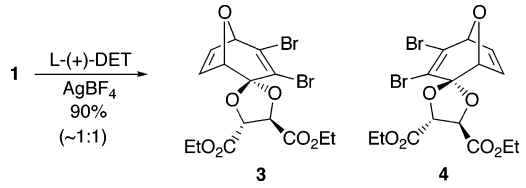
Compound **2** represents a conformationally constrained cycloheptane system that is functionalized at all seven carbons. The enone is a highly versatile synthon and undergoes a wide range of reactions via nucleophilic addition and transition metal promoted cross-coupling.[5] However, our previous preparation of this enone was restricted to the synthesis of the racemic variant which inherently limits its use in the synthesis of natural products. In this paper, we describe the preparation of this enone in both enantiomeric forms through a ketal-based resolution strategy.[6]

This strategy was based on an earlier observation[4] that silver salts also promoted the addition of alcohol based nucleophiles to the tetrabromo cycloadduct. When the alcohol nucleophile is a 1,2-diol, a ketal resulted from

SCHEME 1



SCHEME 2



sequential addition to a presumed allylic cation intermediate. This suggested a resolution strategy whereby a chiral glycol is added to the tetrabromo compound to produce two diastereomeric ketals. Upon separation and hydrolysis, the homochiral enones would be produced. Although there are several chiral diols available, we were attracted to the use of simple tartrate esters as highly economical diols. Toward that end we studied the reaction of diethyl tartate with the tetrabromide **1** in the presence of silver ion (Scheme 2).

Of several different silver salts, silver tetrafluroborate gave the best, reproducible results, delivering the diastereomeric ketals **3** and **4** in a combined yield of 90%. Small amounts of the racemic ketone **2** were also observed in the reaction, likely the result of trace amounts of water in the silver salts. It was also observed that older batches of silver tetrafluroborate led to the production of a *gem*-difluoro adduct but that this product is eliminated with the use of fresh reagent.[7] After removal of the silver salts from the reaction, the two diastereomeric ketals could be separated through careful column chromatography to give an approximately equal amount of each compound.

With the two chiral ketals in hand, conversion to the desired enone building blocks required simple hydrolysis of the ketal. Although tartrate ketals have been used previously for similar resolutions, it is well-known that their removal can be difficult and recourse is often made to the use of reduced forms of the tartrate.[8] It was also observed in this system that hydrolysis to the ketone was difficult, and under normal aqueous, acidic conditions, the ketals were completely stable, even at high acid concentrations and elevated temperatures. Castaldi[9] had previously reported that the use of a large excess of methanesulfonic acid with a small amount of water was an effective protocol for the removal of tartrate-derived ketals. We observed that treatment of ketal **3** or **4** under these conditions led to production of the corresponding enones in moderate yield. Careful optimization (Table 1)

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(7) Silver tetrafluoroborate (99%) was purchased from Strem Chemicals, Inc.

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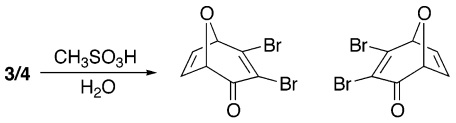
TABLE 1. Optimization of Ketal Hydrolysis



(-) 2 $[\alpha]_D$=-29.2° **(+) 2** $[\alpha]_D$=+28.2°

entry	ketal	scale (mg)	$MeSO_3H$ (equiv)	H_2O (equiv)	time	*T* (°C)	yield (%)
1	**4**	20	144	5	5 h	25	42
2	**4**	20	144	6	5 h	25	70
3	**4**	20	144	8	5 h	25	85
4	**4**	20	144	8	3 h	25	57
5	**4**	20	144	8	7 h	25	59
6	**4**	200	144	8	4 h	25	54
7	**4**	200	144	8	35 min	40	70
8	**4**	200	144	8	45 min	40	75
9	**4**	200	144	8	50 min	40	60
10	**3**	200	144	8	30 min	40	75

of this reaction revealed that the molar equivalents of water and methanesulfonic acid along with the reaction time were critical parameters in controlling the yield of the reaction. Monitoring of the reaction by GC−MS revealed an optimal time-course for the reaction after which the enone product underwent extensive decomposition. Under the optimized set of conditions, the enone could be formed in 85% yield on a 25−50 mg scale. However, attempts to increase the scale to the hundreds of milligrams level resulted in a sharp decrease in the reaction yield. Apparently, increasing the scale of the reaction retarded the rate of hydrolysis to the point that various decomposition reactions became competitive. A slight increase in the temperature of the reaction greatly accelerated the rate of hydrolysis and resulted in good yields of the enone on a larger scale (entries 8 and 9).

With an efficient route to the optically active enone building blocks in hand, it remained to assign the absolute configuration and the optical purity of each isomer. The absolute configuration of tartrate **4** was assigned through the use of X-ray crystallographic analysis which indicated that the absolute configuration of the corresponding enone is that depicted for (+)-**2**.

The absolute configuration of ketal **3** and enone (−)-**2** were assigned by analogy. The optical purity of enones (+)-**2** and (−)-**2** was determined via the *endo* allylic alcohol derivatives[10] through the use of chiral HPLC.[11] The optical purity was shown to be 96% and 97% respectively.

In conclusion, we have developed a route to prepare the previously described racemic enone **2** in both homochiral forms through resolution of a tartrate-derived ketal. Carefully controlled hydrolysis using methanesulfonic acid and a limited amount of water at slightly elevated temperatures was key to producing the enones in good yields. Application of these versatile building blocks to natural product total synthesis is currently underway.

Experimental Section

Spiro[1*S*,5*R*(1*R*,5*S*)-3,4-dibromo-8-oxabicyclo[3.2.1]octa-3,6-diene-2,2′-[1′,3′]dioxolane-4′*R*,5′*R*-dioic acid diethyl ester] (3 and 4). In a glovebox, a flame-dried 50 mL flask was charged with silver tetrafluoroborate (1.02 g, 2.2 equiv), dichloromethane (10 mL), and L-(+)-diethyl tartrate (987 mg, 2.0 equiv). The solution was cooled to −78 °C and allowed to stir for 10 min. Tetrabromide **1** (1.00 g, 1.0 equiv) was dissolved in dichloromethane (10 mL) and added dropwise with stirring into the flask containing the silver tetrafluoroborate and L-(+)-diethyl tartrate. The mixture was rapidly warmed to room temperature by removal of the cooling bath and monitored by TLC until all starting material was consumed. Upon completion of the reaction, cold, saturated sodium bicarbonate solution (20 mL) was added and the mixture filtered through Celite to remove the silver salts. The organic layer was washed with water, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the crude product as a dark red oil. The crude oil was subjected to silica gel column chromatography using 10% ethyl acetate in pentanes to obtain **3** (495 mg, 45%) as a colorless oil and **4** (500 mg, 45%) as colorless crystals.

3: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (dd, J = 4.2 Hz, 1.7 Hz, 1H), 6.36 (dd, J = 3.9 Hz, 2.0 Hz, 1H), 5.14 (d, J = 2.0 Hz, 1H), 5.11 (d, J = 6.1 Hz, 1H), 4.95 (d, J = 1.7 Hz, 1H), 4.85 (d, J = 6.1 Hz, 1H), 4.33−4.22 (m, 4H), 1.31 (dt, J = 11.0 Hz, 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 167.2, 140.4, 135.4, 131.0, 121.2, 108.2, 84.8, 84.5, 78.8, 78.0, 62.5, 62.4, 13.23, 14.19; IR (NaCl) cm^{-1} 2982, 1746, 1606, 1467, 1375, 1293, 1224, 1146, 1104, 1072, 1036, 980, 956, 930, 845, 725 cm^{-1}; EI-HRMS *m*/*z* calcd for $C_{15}H_{16}Br_2O_7$ (M^+) 466.9341, found 466.9349; $[\alpha]^{26}_D$ +1.11. Anal. Calcd for $C_{15}H_{16}Br_2O_7$: C, 38.49; H, 3.45. Found: C, 38.78; H, 3.45.

4: mp 88−89 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (dd, J = 4.4 Hz, 1.6 Hz, 1H), 6.42 (dd, J = 3.7 Hz, 2.2 Hz, 1H), 5.01 (d, J = 6.1 Hz, 1H), 4.96 (d, J = 2.2 Hz, 1H), 4.95 (d, J = 1.7 Hz, 1H), 4.77 (d, J = 6.1 Hz, 1H), 4.33−4.25 (m, 4H), 1.31 (td, J = 6.1 Hz, 1.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 167.2, 140.1, 135.8, 131.4, 121.0, 107.9, 84.6, 84.5, 77.9, 77.6, 62.5, 62.4, 14.23, 14.21; IR (NaCl) cm^{-1} 2982, 1748, 1607, 1469, 1375, 1293, 1223, 1147, 1103, 1036, 929, 725 cm^{-1}; EI-HRMS *m*/*z* calcd for $C_{15}H_{16}Br_2O_7$ (M^+) 466.9341, found 466.9349; $[\alpha]^{26}_D$ −4.40. An analytically pure sample was obtained by recrystallization from 10% ethyl acetate in pentanes. Anal. Calcd for $C_{15}H_{16}Br_2O_7$: C, 38.49; H, 3.45. Found: C, 38.53; H, 3.38.

Typical Procedure for Hydrolysis of Tartrate Ketals. The tartrate ketal (1.0 equiv) was weighed into a 10 mL flask containing a magnetic stir bar. Water (8 equiv) was added, followed by methanesulfonic acid (144 equiv). The flask was capped and heated at 40 °C until no more starting material remained. Upon complete consumption of the starting material as determined by GC−MS, the reaction mixture was poured over a cooled solution of ice (10 g), saturated, aqueous sodium bicarbonate (20 mL), and ethyl acetate (10 mL). The solution was stirred at 0 °C for 15 min and transferred to a separatory funnel. The organic layer was separated and washed with saturated, aqueous sodium bicarbonate (2 × 10 mL). The combined aqueous washes were extracted with ethyl acetate (2 × 20 mL). The combined organics were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography using 20% ethyl acetate in pentanes.

(1*R*,5*S*)-3,4-Dibromo-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one ((−)2). A total of 200 mg of **3** upon hydrolysis and purification yielded (−)-**2** (91 mg, 75%) as white crystals: mp 86−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, J = 5.7 Hz, 2.0 Hz, 1H), 6.57 (dd, J = 5.6 Hz, 2.2 Hz, 1H), 5.37 (d, J = 2.0 Hz, 1H), 5.15 (d, J = 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.6, 149.3, 138.8, 131.4, 120.2, 86.9, 86.7; $[\alpha]^{26}_D$ −29.

(1*S*,5*R*)-3,4-Dibromo-8-oxabicyclo[3.2.1]octa-3,6-dien-2-one ((+)2). A total of 200 mg of **4** upon hydrolysis and purification yielded (+)-**2** (91 mg, 75%) of the enone as white crystals: mp 86−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (dd, J = 5.7 Hz, 2.0 Hz, 1H), 6.58 (dd, J = 5.6 Hz, 2.2 Hz, 1H), 5.38 (d, J = 2.0 Hz, 1H), 5.17 (d, J = 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.7, 149.4, 138.8, 131.5, 120.3, 87.0, 86.8; $[\alpha]^{26}_D$ +28.

(10) The corresponding *endo*-alcohols were prepared by Luche reduction as described in ref 3.

(11) HPLC analysis was performed on a Chiralcel OJ-H column (Daicel Chemical Industries).

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Supporting Information Available: X-ray data for **4**, ^{1}H and ^{13}C NMR for all compounds, and HPLC chromatograms for (+)-**2** and (−)-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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