focus further studies in this area.

Experimental Section

Natural abundance ^{17}O NMR chemical shifts measurements were made in ~30% solutions of cations in $FSO_3H:SbF_5$ (1:1)/SO_2 systems at −65 °C. Typical spectral parameters include 1.25 K data points, a 25-kHz spectral width, and acquisition time of 25 ms. Alfa delays of 30 μs were used to prevent pulse break through. A reasonable quality spectrum was obtained in ~500 000 scans. In view of the small number of data points and rolling baseline, errors in $\delta^{17}O$ measurements are estimated to be ±2 ppm.

Acknowledgment. Support of our work by the National Institutes of Health is gratefully acknowledged.

Registry No. 1 (X = 4-OMe), 41868-76-2; 1 (X = 4-Me), 20122-40-1; 1 (X = H), 19270-10-1; 1 (X = 4-Cl), 20122-41-2; 1 (X = 4-Br), 45709-42-0; 1 (X = 4-F), 39981-36-7; 1 (X = 4-CF_3), 46061-29-4; 1 (X = 3-CF_3), 46060-47-3; ^{17}O, 13968-48-4.

Communications

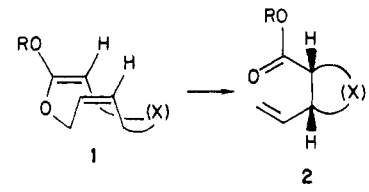
A New Approach to Heterocycles: Synthesis of (±)-*N*-Benzoylmeroquinene Methyl Ester

Summary: A new approach to the total synthesis of *N*-benzoylmeroquinene methyl ester is described and features the stereospecific Claisen rearrangement of the (*E*)-silyl ketene acetal derived from azalactone **7** as the key step in the construction of the disubstituted piperidine ring.

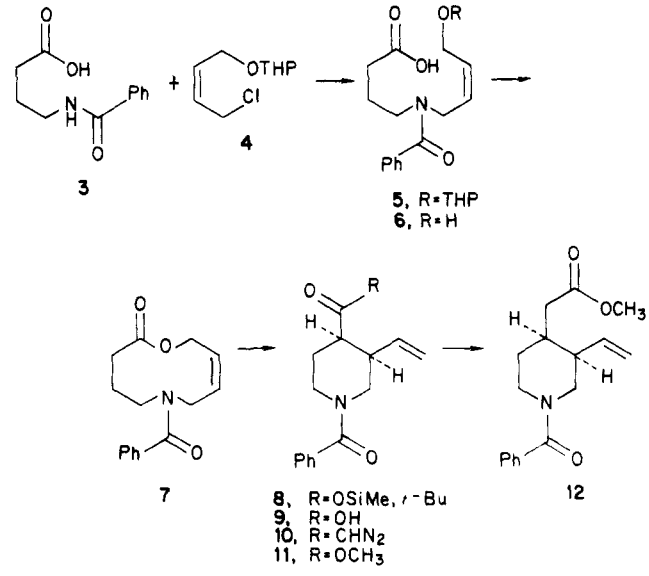
Sir: We have recently reported a general, stereospecific synthesis of *cis*-2-alkenylcycloalkanecarboxylic acids **2** by way of a Claisen-rearrangement-mediated-four-atom ring contraction of macrocyclic ketene acetals **1**.[1] Ketene acetals **1** (X = $(CH_2)_n$, n = 1, 3, 4, 5, 6) proceed through a boat-like transition state to yield exclusively the cis-disubstituted carbocycles **2** (Scheme I). The potential for extending this methodology to the synthesis of heterocycles clearly exists. Substitution of a heteroatom for one of the carbon atoms not participating in the sigmatropic rearrangement of **1** should allow access to heterocycle **2**. In principle, one could synthesize a wide variety of heterocycles using this approach, provided the heteroatom is suitably positioned and can withstand the necessary conditions to effect the Claisen rearrangement. An attractive target for exploring this synthetic approach is the alkaloid derivative *N*-benzoylmeroquinene methyl ester **12**,[2] a key intermediate in several recent total syntheses of *Cinchona* alkaloids, e.g., quinine.[3]

Previous syntheses[2] of **12** established the cis stereorelationship of the two side chains on the piperidine ring by catalytic hydrogenation followed by the subsequent unraveling of a latent vinyl group. In our approach, we anticipated that the Claisen rearrangement of the (*E*)-silyl ketene acetal derived from azalactone **7** should afford the disubstituted piperidine ring with concomitant introduction of the *cis*-3-vinyl moiety. Homologation of the carboxylic acid **9** would then complete the synthesis of **12**. Therefore, the synthesis of **7** became our immediate synthetic goal (Scheme II).

Scheme I



Scheme II



To this end, the dianion of *N*-benzoyl-4-aminobutyric acid (**3**,[5] 2 equiv of NaH, DMF, 0 °C) was treated with *cis*-1-chloro-2-butene 4-tetrahydropyranyl ether (**4**,[6] 1.2 equiv, DMF, 0 → 25 °C, 16 h) to give **5** as an oil in 67% yield. Removal of the tetrahydropyranyl ether[7] (PPTs, methanol, reflux 4 h) gave hydroxy acid **6** in 92% yield. Lactonization of **6** by the procedure of Mukaiyama[8] (2-chloro-1-methylpyridinium iodide, Et_3N, 0.005 M in ace-

(1) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030. We have coined the term "Alicyclic Claisen Rearrangement" to describe this methodology.

(2) For the synthesis of **12**, see the elegant work of the Hoffmann-La Roche group: Uskoković, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571. Prior to this work, compound **12** was available only from meroquinene, a degradation product of cinchonine.[4] Also see: Imanishi, T.; Inoue, M.; Wada, Y.; Hanaoka, M. *Chem. Pharm. Bull.* **1982**, *30*, 1925.

(3) For syntheses of *Cinchona* alkaloids based on utilization of **12**, see: (a) Gutzwiller, J.; Uskoković, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576. (b) Grethe, G.; Lee, H. L.; Mitt, T.; Uskoković, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 581. (c) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1974**, *96*, 8095. (d) Gates, M.; Sugavanam, B.; Schreiber, W. L. *J. Am. Chem. Soc.* **1971**, *93*, 205.

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tonitrile, reflux 42 h) afforded the required azalactone 7[9] in 73% yield after chromatography on silica gel. Subjection of 7 to the usual silylation conditions[1] (1.2 equiv of LDA, 1.2 equiv of t-BuMe$_2$SiCl, THF, −70 °C) produced the expected rearrangement product 8 in 93% yield. Hydrolysis of the silyl ester (2 equiv of HF, 3 N in acetonitrile, 0 °C) gave a single carboxylic acid 9[9] in 92% yield (86% based on 7). None of the trans-3,4-disubstituted isomer of 9 could be detected.[10] Completion of the synthesis by means of the Wolff rearrangement proved uneventful. Treatment of 9 sequentially with sodium hydride and oxalyl chloride (1.0 equiv of each, ether, 0 °C) followed by the addition of this reaction mixture to excess ethereal diazomethane (0 °C, 1 h)[11] gave the diazo ketone 10 as an oil in 83% yield. Without purification, 10 was treated with silver benzoate and triethylamine in methanol[12] (0 °C, 6 h) to afford N-benzoylmeroquinene methyl ester 12 in 77% yield. Ester 12 obtained in this manner was identical in all respects with an authentic sample[13] of 12 kindly provided by Dr. M. R. Uskokovič of Hoffmann-La Roche, Inc. The overall yield of 12 obtained by this route was 25% based on 3.

The methodology reported herein represents a new strategy for heterocycle synthesis. We are currently investigating the application of this approach in the synthesis of the pyrrolidine α-kainic acid and other heterocycles.

Acknowledgment. We appreciate the financial and material support provided by the National Institutes of Health (Grant No. GM2866301). High-field (360 MHz) ^{1}H and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant No. CHE-80-24328). Mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (Grant CHE-82-11164).

Registry No. 3, 35340-63-7; (±)-4, 92127-12-3; (±)-5, 92127-13-4; 6, 92127-14-5; 7, 92127-15-6; (±)-8, 92127-16-7; (±)-9, 92127-17-8; (±)-9 (R = Cl), 92127-20-3; (±)10, 92127-18-9; (±)-11, 92127-19-0; (±)-12, 26013-17-2; quinine, 130-95-0.

(9) Lactone 7: IR (NaCl, neat) 3055, 3025, 2930, 2870, 1748, 1635, 1572, 1490, 1443, 1428, 1395, 1375, 1325, 1280, 1240, 1195, 1157, 1135, 1080, 1055, 1031, 1024, 790, 718, 695, 655 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$, 25 °C) δ 7.33 (br s, 5 H), 5.90–5.43 (m, 2 H), 4.67 (m, 2 H), 4.11 (br d, 2 H, J = 7.5 Hz), 3.26 (br t, 2 H, J = 5.0 Hz), 2.50–2.27 (m, 2 H), 2.13–1.83 (m, 2 H); exact mass calcd for $C_{15}H_{17}O_3N$ 259.1209, found 259.1200; m/e (relative intensity) 259 ($M^{+\cdot}$, 0.21), 216 (1.74), 215 (11.27), 214 (2.10), 187 (3.81), 186 (3.54), 159 (1.00), 158 (2.01), 105 (100.0), 82 (1.28), 78 (2.38), 77 (25.48), 74 (6.32), 69 (1.22), 59 (9.42), 55 (1.27), 54 (1.23), 51 (3.80). Anal. Calcd for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.41. Found: C, 69.36, H, 6.79; N, 5.49. Carboxylic acid 9: mp 48–9 °C; IR (NaCl, neat) 3650–2850, 3040, 3025, 2995, 2925, 2855, 1720, 1595, 1575, 1465, 1450, 1305, 1255, 1180, 1018, 915, 785, 730 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$, 60 °C) δ 7.39 (br s, 5 H), 5.85 (ddd, 1 H, J = 17.21, 10.38, 7.65 Hz), 5.25–5.07 (m, 2 H), 4.44–3.73 (m, 2 H), 3.41 (dd, 1 H, J = 13.12, 2.56 Hz), 3.26 (br t, 1 H, J = 8.81 Hz), 2.90–2.75 (m, 2 H), 2.04–1.89 (m, 1 H), 1.88–1.74 (m, 1 H); ^{13}C NMR (50.31 MHz, $CDCl_3$, 50 °C) δ 177.11, 171.11, 135.86, 134.59, 129.66, 128.41, 126.96, 118.04, 44.46, 40.90, 24.33; exact mass calcd for $C_{15}H_{17}O_3N$ 259.1209, found 259.1216; m/e (relative intensity) 259 ($M^{+\cdot}$, 2.69), 218 (2.39), 154 (2.73), 122 (2.93), 106 (4.11), 105 (60.22), 77 (17.87), 51 (2.89), 40 (7.89). Anal. Calcd for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.41. Found: C, 69.40; H, 6.74; N, 5.27.

(10) Product stereochemical integrity was confirmed by HPLC and ^{1}H NMR (360 MHz) analysis of the methyl ester 11 (CH_2N_2, ether, 0 °C) derived from the crude product 9. A single methyl ester peak was observed at δ 3.63, and HPLC analysis showed no other isomers. The presumed stereochemical assignment of 9 was confirmed by its successful conversion to 2.

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(13) The ^{1}H NMR (90 and 360 MHz), ^{13}C NMR (50.31 MHz), IR, and MS spectra and HPLC and TLC (three solvent systems) chromatograms were compared.

(14) Maude Hammond Fling Fellow, 1982–84, from the University of Nebraska.

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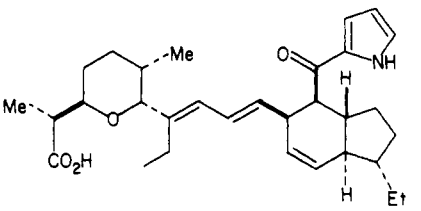
Polysubstituted Dihydropyrans via the Enolate Claisen Rearrangement. A Stereocontrolled Route to *C*-Pyranosides

Summary: A new method for the stereoselective synthesis of dihydropyrans of a variety of substitution patterns is described, involving [3,3]-sigmatropic reorganizations of 6-alkenyl-4-oxapyran-2-ones of general structure 1 or 3 to the product dihydropyrans (2 or 4, respectively).

Sir: The polysubstituted hydropyran nucleus is a structural subunit in a number of recently isolated natural products of chemical and biological interest. Selected examples include the ionophore antibiotic X-14547A,[2] the



X-14547A

antifungal agent ambruticin,[3] and the structurally daunting marine natural product palytoxin.[4] In each of these there exist one or more hydropyran units, formally classified as *C*-pyranosides, wherein the C(2) and C(6) positions flanking the ring oxygen have carbon side-chain substituents. We report herein a stereocontrolled route to the *C*-pyranoside system.[5]

(1) (a) Research Fellow of the Alfred P. Sloan Foundation. (b) Recipient of an NSF Presidential Young Investigator Award.

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