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Cycloisomerization of Conjugated Trienones and Isomeric 2*H*-Pyrans: Unified Strategy toward Cyclopenta[*b*]furans

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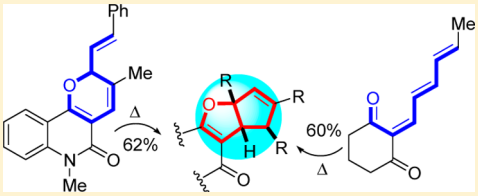
Supporting Information

ABSTRACT: Conjugated trienones and isomeric 2*H*-pyrans were found to engage in a novel cycloisomerization cascade toward cyclopenta[*b*]furan derivatives. Knoevenagel chemistry and pericyclic reactions meet again to expand the polyene-carbonyl manifold.

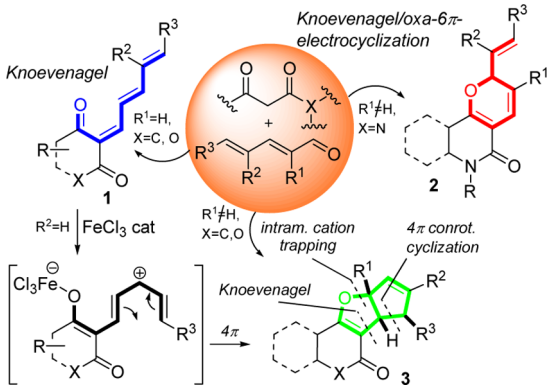


Cycloisomerization reactions do not cease to amaze chemists who stand still trying to grasp the circle dance of atoms in their molecules. Indeed Nature also makes use of these atom-economical transformations to construct many of the rings found embedded in its precious products. One notable example of this is the pericyclic oxa-6π-electrocyclization reaction of dienone (or dienal) structures to yield the well-known 2*H*-pyran isomers. This reversible process is usually masked by subsequent transformations, mostly [4 + 2] cycloadditions, accounting for the biosynthesis of xanthipungolide, torreyanic acid, epoxyquinols A−C, pinnatal, and so many other elegant natural molecules of interest.[1−3]

The domino Knoevenagel condensation/oxa-6π-electrocyclization reaction between enals and 1,3-dicarbonyl substrates, usually referred to as formal [3 + 3] cycloaddition, has become a very useful strategy for the synthesis of natural 2*H*-pyran-containing compounds.[4,5] Our studies on this condensation using $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes revealed that, depending on the substitution pattern and electronic properties, apart from the expected π-conjugated dicarbonyl products and their 2*H*-pyran isomers (**1** and **2**), previously unrelated cyclopenta[*b*]furan isomers of type **3** can also be obtained (Scheme 1).[6] To account for the formation of these unexpected products, a domino Knoevenagel/cationic bicyclization pathway was proposed featuring a pentadienyl-cyclopentenyl cation rearrangement at the end of the polyene chain of the putative, nonisolable, trienone intermediates. Indeed, iron(III) chloride was shown to catalyze the isomerization of stable isolable trienones of type **1** into these heterocyclic isomers (**3**), and the process was hence classified as an interrupted vinylogous iso-Nazarov reaction.[7]

Due to the wide application of molecular switches in the fabrication of novel materials and devices, the dienone/2*H*-pyran isomerism has received considerable attention.[8,9] Krasnaya and Hsung have both independently provided

Scheme 1. Manifold of the Knoevenagel Chemistry Using 1,3-Dicarbonyl Substrates and $\alpha,\beta,\gamma,\delta$-Unsaturated Aldehydes



examples of dienones that rearrange to their pyranic isomers upon thermal treatment.[10,11] In order to test whether vinylogous systems of type **1** behave in such a way, a toluene solution of model substrate **1a**, prepared via Knoevenagel condensation between 1,3-cyclohexanedione and sorbaldehyde, was heated under reflux (Scheme 2A). To our surprise, after 30 h of heating, cyclopenta[*b*]furan isomer **3a** was found as the only isolable product of the reaction. The same reactivity profile was found for other related substrates (Scheme 2B). Although the use of higher-boiling solvents or sealed systems provided faster transformations, marked reduced yields ensued. The possibility to incorporate the Knoevenagel condensation and cycloisomerization process into a one-pot transformation was

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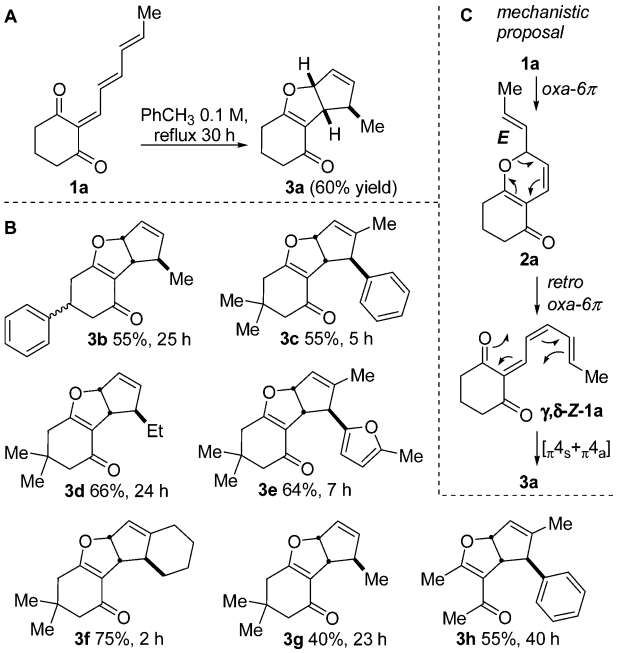
Scheme 2. Thermal Isomerization of Conjugated Trienones 1 to Cyclopenta[*b*]furan Derivatives 3



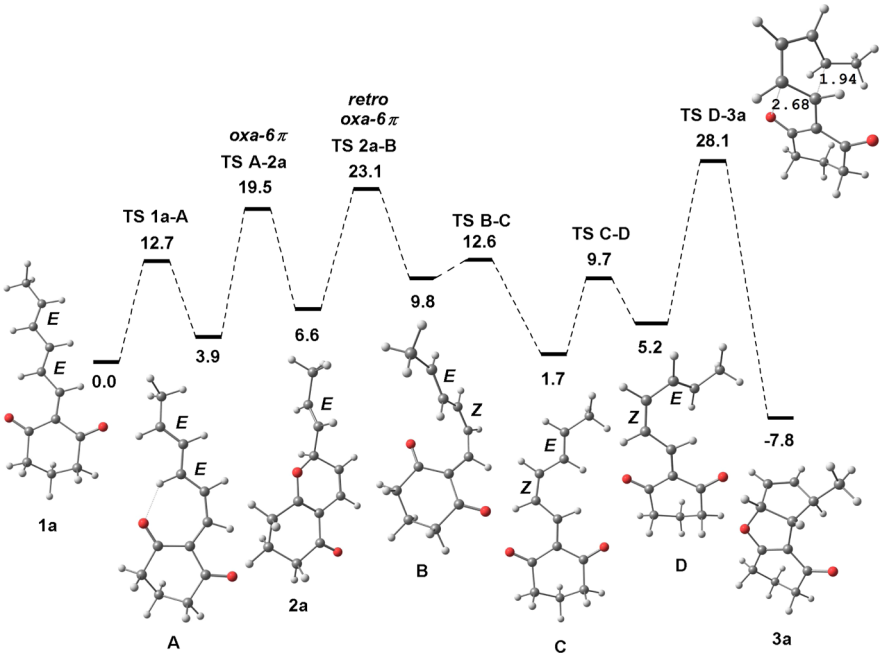
explored as well, but unfortunately, no suitable experimental conditions for making it a valuable process could be found.

Although only moderate yields could be obtained, indeed more efficient transformations were found using our previously developed acid-promoted approach to these cyclopenta[*b*]furan derivatives;[7,12] from a mechanistic viewpoint we were completely amazed by this notable cycloisomerization. To account for cyclopenta[*b*]furan formation, a mechanistic proposal was elaborated indeed involving originally sought 2*H*-pyran isomers as intermediates (Scheme 2C). An initial oxa-6π-electrocyclic ring closure/opening sequence, similar to that proposed to account for the isomerization of retinals,[13] would provide a reactive γ,δ-*Z*-diastereomer of the trienone **1a** substrate. Strain could then force the polyene chain to a conformation in which it is dissected into two 4πe^- moieties. Intramolecular $[{}_{\pi}4_a + {}_{\pi}4_s]$ cycloaddition would then afford cyclopenta[*b*]furan product **3a**. ^{1}H NMR monitoring of these reactions carried out in toluene-d_8 at 100 °C showed no evidence of any of the proposed intermediates. DFT calculations at the M06/6-31+G** level of theory were then performed to assess the feasibility of the proposed pathway (Scheme 3 and Supporting Information; for other DFT functionals, also see Supporting Information).[14] Overall, the bicyclization of substrate **1a** into cyclopenta[*b*]furan isomer **3a** takes six elementary steps and liberates 7.8 kcal/mol of Gibbs free energy: (*i*) conversion of *s-trans*/*s-trans E*/*E* **1a** into the *s-cis*/*s-trans E*/*E* isomer **A**; (*ii*) oxa-6π electrocyclization to give **2a**; (*iii*) retro oxa-6π leading to the *s-cis*/*s-trans Z*/*E* isomer **B**; (*iv*) conversion of **B** into the *s-trans*/*s-trans Z*/*E* isomer **C**; (*v*) formation of the *s-trans*/*s-cis Z*/*E* isomer **D**; and (*vi*) $[{}_{\pi}4_a + {}_{\pi}4_s]$ cycloaddition giving rise to the final product **3a**. As shown by the lengths of the forming C−O and C−C bonds in **TS D-3a** (2.68 and 1.94 Å respectively), the construction of the two rings occurs in an asynchronous fashion in favor of the cyclopentene framework. This last step is the rate determining one ($\Delta G^{\ddagger}_{298}$ = 28.1 kcal/mol).

Our unexpected findings made us revisit the original tandem Knoevenagel/polycyclization reaction between β-diketones or β-ketoesters and α-substituted dienals, for which conjugated trienones were proposed as direct precursors of the cyclopenta-[*b*]furan products **3**, and 2*H*-pyrans of type **2** were regarded rather as products of an unrelated dead-end pathway.[6a] In order to find evidence of any intermediate that could be involved, condensation between model substrates dimedone (**4**) and 2-methyl-5-phenyl-penta-2,4-dienal (**5**) was carried out in an NMR tube (Figure 1).

As soon as the reaction commenced and before any product **3i** was produced, ^{1}H NMR monitoring indeed revealed the

Scheme 3. Calculated Energy Profile (ΔG_{298}, kcal/mol) for the Bicyclization of Conjugated Trienone 1a



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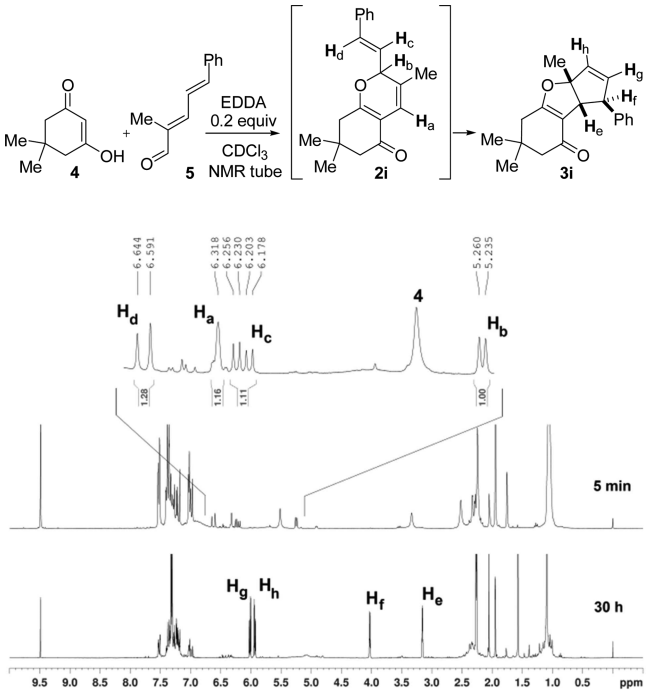
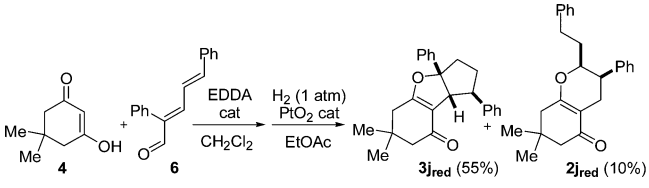


Figure 1. ^{1}H NMR Monitoring of the Tandem Knoevenagel–Bicylization Sequence toward Cyclopenta[*b*]furans (EDDA = ethylenediammonium diacetate).

presence of a molecular species that was gradually consumed and completely depleted after 30 h (Figure 1). This presumable intermediate gives rise to signals which can be tentatively attributed to the structure of 2*H*-pyran **2i**. The uncrowded vinyl region of the ^{1}H NMR spectrum features a broad singlet at 6.32 ppm (H_a), two doublets centered at 6.62 and 5.25 ppm (H_d and H_b, J = 16.0 and 7.5 Hz, respectively), and a doublet of doublets at 6.22 ppm (H_c, J = 16.0, 7.5 Hz). In addition, the oxygen bearing methine carbon would account for the ^{13}C NMR signal at 81.1 ppm (see Supporting Information). Since all attempts to isolate this intermediate foundered, possibly due to rapid isomerization to product **3i**, we envisioned that hydrogenation would allow its trapping.[15] After considerable experimentation using different aldehydes and dicarbonyl substrates, pyran $\mathbf{2j_{red}}$ could be isolated in low yield along with expected reduced cyclopenta[*b*]furan $\mathbf{3j_{red}}$ when the reaction between dimedone (**4**) and 2,5-diphenyl-penta-2,4-dienal (**6**) was interrupted before completion and submitted to hydrogenation under heterogeneous conditions using Adam's catalyst (Scheme 4).

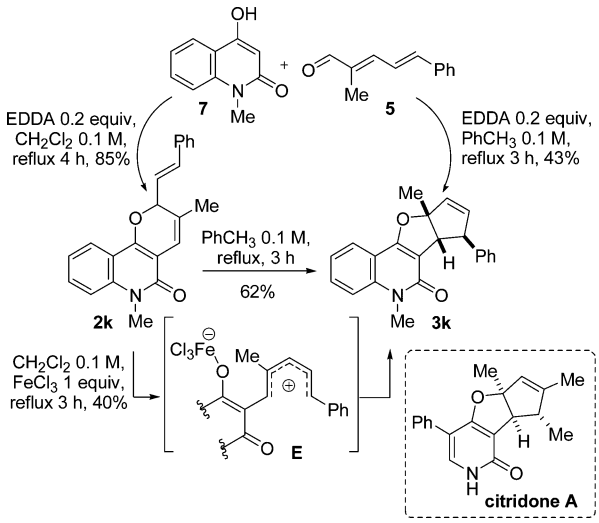
This finding that 2*H*-pyrans could be transient intermediates en route to cyclopenta[*b*]furans prompted us to evaluate whether the cycloisomerization of stable, isolable 2*H*-pyrans may be feasible. As a proof-of-concept, compound **2k** was

Scheme 4. Further Evidence for the Intermediacy of 2*H*-Pyrans en Route to Cyclopenta[*b*]furan Isomers



chosen as the model substrate (Scheme 5). This 2*H*-pyran was prepared via Knoevenagel condensation between aldehyde **5**

Scheme 5. Rearrangement of a Stable 2-Vinyl-2*H*-pyran



and 4-hydroxy-1-methyl-2(1*H*)-quinolone (**7**) as previously reported.[6a] When a toluene solution of **2k** was subjected to reflux conditions, cyclopenta[*b*]furoquinolone **3k** was indeed found as the only isolable product in 62% yield (Scheme 5). In addition, the one-pot Knoevenagel condensation/cycloisomerization sequence, in this case, was shown to be accessible (43% yield). The isomerization of pyran **2k** could also be promoted using ferric chloride (1 equiv) in dichloromethane at reflux, albeit in lower yield (40%). In this case, the reaction would proceed through initial Lewis acid promoted heterolytic C–O bond cleavage generating key polyenyl cation **E** which, after a $4\pi e^{-}$ conrotatory electrocyclization and subsequent stereoselective trapping of the brand new cyclopentenyl cation intermediate by enolic oxygen, would provide *cis*-fused cyclopenta[*b*]furan product **3k**.

In summary, a novel cycloisomerization pathway viable for Knoevenagel chemistry was disclosed. Trienones and 2*H*-pyrans were found to smoothly rearrange to previously unrelated isomers, cyclopenta[*b*]furans. Indeed, this heterocyclic scaffold is widespread in Nature.[16] Taking into account the ease with which these assemblies are stereoselectively constructed from simple precursors, the question rises as to whether this approach could account for the biosynthetic origin of natural products such as citridone A (Scheme 5),[17] which shares the same tricyclic cyclopentafuropyridone core present in product **3k**. Efforts to clarify this scenario are underway.

EXPERIMENTAL SECTION

Unsaturated aldehydes **5** and **6** have been previously prepared by our group.[6]

General Procedure for the Preparation of Substrates 1 and 2 via Condensation of 1,3-Dicarbonyl Compounds and Unsaturated Aldehydes. A mixture of 1,3-dicarbonyl compound (1 mmol), unsaturated aldehyde (1 mmol, 1 equiv), and 1,2-ethylenediammonium diacetate (EDDA, 36 mg, 0.2 mmol) in CH_2Cl_2 (5.0 mL, 0.2 M) was heated at reflux until complete consumption of the aldehyde substrate (TLC monitoring, approximately 3–4 h). The solvent was then evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (eluent hexanes/ethyl acetate) to afford the desired unsaturated substrate **1** or **2**. Conjugated dicarbonyl substrates **1a–h**

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and 2*H*-pyran substrate **2k** have been previously prepared by our group using this protocol.[6,7] For the ^{1}H NMR monitoring of the tandem Knoevenagel−bicylization sequence between dicarbonyl substrate **4** and unsaturated aldehyde **5** toward cyclopenta[*b*]furan **3i**,[6b] this same protocol was used employing $CDCl_3$ as solvent instead of CH_2Cl_2.

General Procedure for the Thermal Cycloisomerization toward Cyclopenta[*b*]furans 3. A solution of conjugated dicarbonyl substrate **1** or 2*H*-pyran **2** (1 mmol) in toluene (10.0 mL, 0.1 M) was heated at reflux until complete consumption of the substrate (TLC monitoring). The solvent was then evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (eluent hexanes/ethyl acetate) to afford the following compounds.

Cyclopenta[b]furan ***3a***.[7] Yield 114 mg (60%). Colorless to pale yellow solid. Mp 46.0−47.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02 (dd, J = 5.6 Hz, J = 2.2 Hz, 1H), 5.82 (dt, J = 8.6 Hz, J = 1.8 Hz, 1H), 5.74 (dt, J = 5.6 Hz, J = 2.0 Hz, 1H), 3.27 (dq, J = 8.5 Hz, J = 1.8 Hz, 1H), 2.84 (qquint, J = 7.3 Hz, J = 1.9 Hz, 1H), 2.39 (td, J = 6.4 Hz, J = 1.6 Hz, 2H), 2.32 (t, J = 6.3 Hz, 2H), 2.00 (quint, J = 6.4 Hz, 2H), 1.18 (d, J = 7.3 Hz, 3H).

Cyclopenta[*b*]furans 3b.[7] Yield 147 mg (55%). Colorless solid. Mp 70.0−71.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.29 (overlapping m, 4H), 7.28−7.20 (overlapping m, 6H), 6.08−6.02 (overlapping m, 2H), 5.92−5.84 (overlapping m, 2H), 5.80−5.72 (overlapping m, 2H), 3.47−3.27 (overlapping m, 4H), 2.95−2.83 (overlapping m, 2H), 2.67−2.54 (overlapping m, 8H), 1.23−1.17 (overlapping m, 6H).

Cyclopenta[b]furan ***3c***.[6a] Yield 162 mg (55%). Pale yellow solid. Mp 95.0−96.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.27 (m, 2H), 7.23−7.17 (m, 3H), 5.90 (dm, J = 8.5 Hz, 1H), 5.67 (q, J = 1.6 Hz, 1H), 3.83 (bs, 1H), 3.58 (dm, J = 8.3 Hz, 1H), 2.31−2.26 (m, 2H), 2.25−2.22 (m, 2H), 1.65 (bs, 3H), 1.11 (s, 3H), 1.08 (s, 3H).

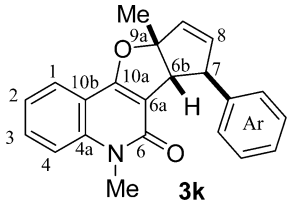
Cyclopenta[b]furan ***3d***.[7] Yield 135 mg (66%). Colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.09−6.01 (m, 1H), 5.84−5.74 (m, 2H), 3.34 (dm, J = 8.4 Hz, 1H), 2.81−2.71 (m, 1H), 2.24 (bs, 2H), 2.19 (bs, 2H), 1.67−1.38 (m, 2H), 1.08 (bs, 3H), 1.06 (bs, 3H), 0.96 (t, J = 7.3 Hz, 3H).

Cyclopenta[b]furan ***3e***.[7] Yield 191 mg (64%). Colorless to pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.00 (d, J = 2.9 Hz, 1H), 5.89 (dm, J = 8.2 Hz, 1H), 5.85 (d, J = 2.2 Hz, 1H), 5.58−5.54 (m, 1H), 3.84 (bs, 1H), 3.78 (bd, J = 8.3 Hz, 1H), 2.27 (bs, 2H), 2.25−2.19 (overlapping signals, 5H), 1.69 (s, 3H), 1.09 (s, 3H), 1.07 (s, 3H).

Cyclopenta[b]furan ***3f***.[7] Yield 194 mg (75%). Pale yellow solid. Mp 98.0−99.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.72 (dtd, J = 8.8 Hz, J = 2.2 Hz, J = 0.6 Hz, 1H), 5.41 (q, J = 1.8 Hz, 1H), 3.31 (dq, J = 8.8 Hz, J = 1.8 Hz, 1H), 2.50 (dm, J = 13.2 Hz, 1H), 2.42−2.31 (m, 2H), 2.25 (d, J = 1.3 Hz, 2H), 2.20 (s, 2H), 1.97 (btd, J = 13.2 Hz, J = 5.4 Hz, 1H), 1.90−1.79 (m, 1H), 1.79−1.69 (m, 1H), 1.37 (qt, J = 13.3 Hz, J = 3.3 Hz, 1H), 1.17 (qt, J = 12.9 Hz, J = 3.8 Hz, 1H), 1.08 (s, 3H), 1.07 (s, 3H), 0.98 (qd, J = 13.1 Hz, J = 3.4 Hz, 1H).

Cyclopenta[b]furan ***3g***.[7] Yield 109 mg (40%). Colorless to pale yellow solid. Mp 42.0−43.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.02 (dd, J = 5.6 Hz, J = 2.2 Hz, 1H), 5.84 (dt, J = 8.5 Hz, J = 2.0 Hz, 1H), 5.74 (dt, J = 5.6 Hz, J = 2.0 Hz, 1H), 3.29 (dq, J = 8.5 Hz, J = 1.8 Hz, 1H), 2.84 (qquint, J = 7.1 Hz, J = 2.2 Hz, 1H), 2.24 (d, J = 1.6 Hz, 2H), 2.20 (bs, 2H), 1.18 (d, J = 7.3 Hz, 3H), 1.08 (s, 3H), 1.06 (s, 3H).

Cyclopenta[b]furan ***3h***. Yield 171 mg (55%). Colorless to pale yellow liquid. IR (film) (cm^{-1}): 3024, 2918, 1665, 1614, 1589, 1377, 1217. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36−7.27 (m, 2H), 7.25−7.18 (m, 1H), 7.18−7.11 (m, 2H), 5.75 (dm, J = 8.7 Hz, 1H), 5.66−5.61 (m, 1H), 3.76 (dm, J = 8.7 Hz, 1H), 3.67 (bs, 1H), 2.23 (bd, J = 1.2 Hz, 3H), 2.18 (s, 3H), 1.58 (bs, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.4 (C), 167.1 (C), 150.1 (C), 143.1 (C), 128.6 (2 × CH), 127.3 (2 × CH), 126.5 (CH), 124.3 (CH), 116.9 (C), 91.5 (CH), 63.0 (CH), 55.8 (CH), 29.6 (CH_3), 15.3 (CH_3), 15.2 (CH_3). HRMS (ESI) m/z calcd for $C_{17}H_{18}O_2Na$ [M + Na]$^+$ 277.1199, found 277.1191.



3k

Cyclopenta[b]furan ***3k***. Yield 204 mg (62%). Pale yellow solid. Mp 119.0−120.0 °C. IR (film) (cm^{-1}): 3057, 3026, 2970, 2924, 1655, 1636, 1595, 1354, 1094. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78 (dd, J = 7.8 Hz, J = 1.3 Hz, 1H, 1-H), 7.57 (ddd, J = 8.6 Hz, J = 7.6 Hz, J = 1.4 Hz, 1H, 3-H), 7.50−7.43 (m, 2H, Ar−H), 7.41−7.31 (overlapping m, 3H, 4-H, Ar−H), 7.28−7.18 (overlapping m, 2H, 2-H, Ar−H), 6.11−6.04 (m, 2H, 8-H, 9-H), 4.33 (bs, 1H, 7-H), 3.73 (s, 3H, N−CH_3), 3.55 (bd, J = 1.7 Hz, 1H, 6b-H), 1.71 (s, 3H, 9a-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.3 (C, C-6), 160.0 (C, C-10a), 143.6 (C, Ar), 140.6 (C, C-4a), 137.1 (CH, C-8), 133.8 (CH, C-9), 130.8 (CH, C-3), 128.5 (2 × CH, Ar), 127.3 (2 × CH, Ar), 126.5 (CH, Ar), 123.4 (CH, C-1), 121.4 (CH, C-2), 114.3 (CH, C-4), 112.9 (C, C-10b), 111.4 (C, C-6a), 104.3 (C, C-9a), 58.8 (CH, C-6b), 56.5 (CH, C-7), 28.8 (CH_3, N−CH_3), 25.5 (CH_3, C9a-CH_3). HRMS (ESI) m/z calcd for $C_{22}H_{20}NO_2$ [M + H]$^+$ 330.1489, found 330.1479.

Tandem Condensation/Hydrogenation for the Trapping of 2*H*-Pyran Intermediate en Route to Cyclopenta[*b*]furans. A mixture of 1,3-dicarbonyl substrate **4** (140 mg, 1 mmol), unsaturated aldehyde **6** (234 mg, 1 mmol), and EDDA (36.0 mg, 0.2 mmol) in CH_2Cl_2 (5.0 mL) was heated at reflux for 4 h. The solvent was then evaporated under reduced pressure, and the residue was passed through a short path of silica gel (eluted with hexanes/ethyl acetate). The solvent was then evaporated under reduced pressure, and the crude mixture was dissolved in ethyl acetate (50 mL). To this solution was added PtO_2 (30 mg), and the resulting suspension was degassed three times (three vacuum/hydrogen cycles to remove air). The suspension was vigorously stirred under a hydrogen atmosphere (balloon, ca.1 atm) at room temperature for 30 min, filtered through Celite, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/ethyl acetate) to afford products $\mathbf{2j}_{red}$ (36 mg, 10% yield) and $\mathbf{3j}_{red}$ (197 mg, 55% yield).

2H-Pyran $\mathbf{2j}_{red}$. Colorless solid. Mp 140.0−141.0 °C. IR (KBr) (cm^{-1}): 3082, 3059, 3022, 2951, 2926, 2907, 1637, 1491, 1447, 1398, 1213, 1140. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36−7.16 (overlapping m, 10H), 3.78 (bs, 1H), 3.48 (bd, J = 6.9 Hz, 1H), 2.46−2.39 (overlapping m, 4H), 2.32−2.05 (overlapping m, 4H), 1.16 (s, 3H), 1.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 194.2 (C), 174.8 (C), 144.0 (C), 142.5 (C), 128.4 (2 × CH), 128.3 (2 × CH), 127.6 (CH), 127.0 (2 × CH), 125.8 (CH), 124.7 (2 × CH), 115.1 (C), 103.8 (C), 59.4 (CH), 51.0 (CH_2), 50.4 (CH), 39.9 (CH_2), 37.7 (CH_2), 34.1 (C), 29.8 (CH_2), 29.0 (CH_3), 28.0 (CH_3). HRMS (ESI) m/z calcd for $C_{25}H_{26}NaO_2$ [M + Na]$^+$ 381.1825, found 381.1815.

Cyclopenta[b]furan $\mathbf{3j}_{red}$. Colorless liquid. IR (film) (cm^{-1}): 3059, 3026, 2953, 2926, 2907, 1625, 1392, 1217. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35−7.11 (overlapping m, 8H), 7.10−7.02 (overlapping m, 2H), 4.29 (dt, J = 10.0 Hz, J = 3.5 Hz, 1H), 3.20 (td, J = 7.0 Hz, J = 3.5 Hz, 1H), 2.81−2.45 (overlapping m, 4H), 2.43−2.22 (overlapping m, 4H), 1.84−1.53 (m, 2H), 1.11 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 197.7 (C), 168.8 (C), 141.1 (C), 139.9 (C), 128.4 (2 × CH), 128.28 (2 × CH), 128.26 (2 × CH), 127.9 (2 × CH), 126.7 (CH), 125.9 (CH), 109.7 (C), 79.2 (CH), 50.5 (CH_2), 42.3 (CH_2), 40.2 (CH), 32.1 (C), 32.0 (CH_2), 31.0 (CH_2), 28.5 (CH_3), 28.1 (CH_3), 21.4 (CH_2). HRMS (ESI) m/z calcd for $C_{25}H_{28}NaO_2$ [M + Na]$^+$ 383.1981, found 383.1969.

Lewis Acid Promoted Cycloisomerization of 2*H*-pyran 2k. To a solution of pyran derivative **2k**[6a] (329 mg, 1 mmol) in CH_2Cl_2 (10.0 mL, 0.1 M), $FeCl_3$ (167 mg, 1 mmol) was added. The mixture was heated at reflux until complete consumption of the substrate (TLC monitoring, approximately 3 h). The solvent was then evaporated under reduced pressure, and the residue was purified by

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flash column chromatography on silica gel (hexanes/ethyl acetate) to afford cyclopenta[*b*]furan **3k** (132 mg, 40% yield).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H NMR spectra of known compounds prepared by new methodology, and ^{1}H, ^{13}C, and 2D NMR spectra for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00818.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For a review on biosynthetic and biomimetic electrocyclizations, see: (a) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757 and references cited therein. The interested reader should also consult: (b) Biomimetic Organic Synthesis, 2 Vols.; Poupon, E., Nay, B., Eds.; Wiley-VCH Verlag: Weinheim, 2011. (c) Miller, A. K.; Trauner, D. *Synlett* **2006**, 2295. (d) Moses, J. E.; Baldwin, J. E.; Brückner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670.

(2) For reviews on transition-metal-catalyzed and/or electrophile-promoted cycloisomerizations, see: (a) Yamamoto, Y. *Chem. Rev.* **2012**, *112*, 4736. (b) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (c) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (d) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. (e) Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011. (f) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

(3) For a recent review on catalytic enantioselective cycloisomerizations, see: Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899.

(4) (a) Riveira, M. J.; Mischne, M. P. *Synth. Commun.* **2013**, *43*, 208. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, *1*, 23 and references cited therein.

(5) For a recent review on domino reactions based on Knoevenagel condensations, see: Voskressensky, L. G.; Festa, A. A.; Varlamov, A. V. *Tetrahedron* **2014**, *70*, 551.

(6) (a) Riveira, M. J.; Mischne, M. P. *Chem.—Eur. J.* **2012**, *18*, 2382. (b) Riveira, M. J.; Gayathri, C.; Navarro-Vázquez, A.; Tsarevsky, N. V.; Gil, R. R.; Mischne, M. P. *Org. Biomol. Chem.* **2011**, *9*, 3170.

(7) Riveira, M. J.; Mischne, M. P. *J. Org. Chem.* **2014**, *79*, 8244.

(8) Spirochromenes comprise the most important class of photochromic 2*H*-pyrans.

(9) (a) Buback, J.; Kullmann, M.; Langhojer, F.; Nuernberger, P.; Schmidt, R.; Würthner, F.; Brixner, T. *J. Am. Chem. Soc.* **2010**, *132*, 16510. (b) Mandal, S.; Parida, K. N.; Samanta, S.; Moorthy, J. N. *J. Org. Chem.* **2011**, *76*, 7406. (c) Huang, C.-N.; Kuo, P.-Y.; Lin, C.-H.; Yang, D.-Y. *Tetrahedron* **2007**, *63*, 10025. For the first report on the isomerization of a dienone to an α-pyran, see: (d) Marvell, E. N.; Caple, G.; Gosink, T. A.; Zimmer, G. *J. Am. Chem. Soc.* **1966**, *88*, 619.

(10) Krasnaya, Z. A. *Chem. Heterocycl. Compd.* **1999**, *35*, 1255.

(11) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.-L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem.* **2003**, *68*, 1729.

(12) Products **3c** and **3f** could not be previously obtained using either ferric chloride as the catalyst or a Brønsted acid such as camphorsulfonic acid; they undergo further rearrangement to a different isomer. See ref 7.

(13) (a) Álvarez, R.; Vaz, B.; Gronemeyer, H.; de Lera, A. R. *Chem. Rev.* **2014**, *114*, 1. (b) Zhu, Y.; Ganapathy, S.; Liu, R. S. H. *J. Org. Chem.* **1992**, *57*, 1110. (c) Kluge, A. F.; Lillya, C. P. *J. Org. Chem.* **1971**, *36*, 1977. (d) Kluge, A. F.; Lillya, C. P. *J. Org. Chem.* **1971**, *36*, 1988.

(14) Frisch, M. J. et al. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.

(15) For previous examples on the hydrogenation of 2*H*-pyrans obtained via Knoevenagel condensation between β-ketoesteres and α,β-unsaturated aldehydes, see: Peng, W.; Hirabaru, T.; Kawafuchi, H.; Inokuchi, T. *Eur. J. Org. Chem.* **2011**, 5469.

(16) (a) Ribeiro, N.; Thuaud, F.; Nebigil, C.; Désaubry, L. *Bioorg. Med. Chem.* **2012**, *20*, 1857 and references therein. (b) Magnus, P.; Freund, W. A.; Moorhead, E. J.; Rainey, T. *J. Am. Chem. Soc.* **2012**, *134*, 6140. (c) Fletcher, C. J.; Blair, D. J.; Wheelhouse, K. M. P.; Aggarwal, V. K. *Tetrahedron* **2012**, *68*, 7598. (d) Li, N.; Di, L.; Gao, W.-C.; Wang, K.-J.; Zu, L.-B. *J. Nat. Prod.* **2012**, *75*, 1723. (e) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560. (f) Enomoto, M.; Kuwahara, S. *J. Org. Chem.* **2006**, *71*, 6287. (g) Che, Y.; Araujo, A. R.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **2005**, *68*, 435. (h) Gerard, B.; Jones, G., II; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 13620. (i) Larock, R. C.; Lee, N. H. *J. Org. Chem.* **1991**, *56*, 6253.

(17) (a) Miyagawa, T.; Nagai, K.; Yamada, A.; Sugihara, Y.; Fukuda, T.; Fukuda, T.; Uchida, R.; Tomoda, H.; Ōmura, S.; Nagamitsu, T. *Org. Lett.* **2011**, *13*, 1158. (b) Fotiadou, A. D.; Zografos, A. L. *Org. Lett.* **2011**, *13*, 4592.

DOI: 10.1021/acs.joc.5b00818
J. Org. Chem. 2015, 80, 6515−6519