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Acid-Catalyzed Formal Cycloaddition of α,β-Unsaturated Carbonyls with Epoxides: Dioxepines or Acetals?

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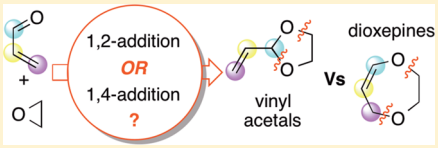
Supporting Information

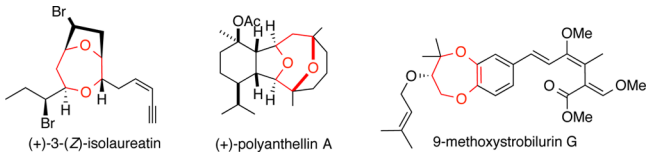
ABSTRACT: It has been recently reported that the reaction of α,β-unsaturated carbonyl derivatives with epoxides in the presence of a homogeneous acid catalyst readily delivers the corresponding dioxepines via formal (4 + 3) cycloaddition. We report herein that the same apparent reactivity can be triggered via heterogeneous catalysis. Characterization of products by means of NMR correlation experiments and DFT modeling revealed, however, that products are the acetals of the unsaturated reagent rather than the desired heterocycles.



Catalytic cycloadditions are a powerful synthetic tool for the straightforward construction of complex polycyclic frameworks from readily available precursors.[1] Regarding medium-sized rings, their broad domain of applications pushed the development of a variety of elegant methods to access seven-membered cyclic cores by either a (4 + 3) or a (5 + 2) strategy.[1] While extremely efficient protocols exist to form carbocycles, the incorporation of heteroatoms within the ring remains synthetically challenging.[2]

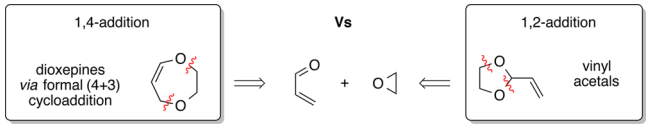
1,4-Dioxepines are well-known for their biological properties (Scheme 1),[3] and their preparation usually requires substrate prefunctionalization and multistep syntheses, ultimately affecting the panel of readily accessible motifs and the environmental cost of the process.[4] Recently introduced has been the possibility to synthesize these heterocycles by formal cycloaddition between an α,β-unsaturated carbonyl compound and an epoxide in the presence of a Lewis acid as homogeneous catalyst (Scheme 2, left).[5]

Scheme 1. 1,4-Dioxepine Core in Natural Products



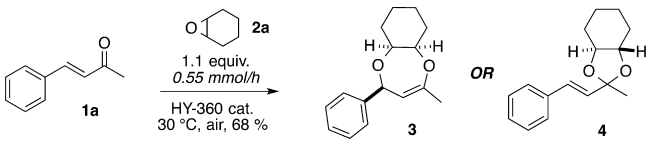
As part of our ongoing interest toward the use of zeolites as an efficient tool to develop eco-friendly synthetic processes,[6] we wished to develop a catalytic synthesis of dioxepines via formal (4 + 3) cycloaddition using these heterogeneous solid acids. On the basis of our studies, we report herein that products of these reactions are vinyl acetals rather than the originally proposed dioxepines (Scheme 2, right).

Scheme 2. Comparison of Possible Outcomes Reacting Epoxides with α,β-Unsaturated Carbonyls



As a model reaction, we attempted the synthesis of the reported dioxepine **3**[5] by stirring 3 mmol of ketone **1a** with 1.1 equiv. of cyclohexene oxide **2a** in the presence of a catalytic amount of a solid acid at 30 °C for 8 h (Scheme 3). Epoxide **2a** was slowly added to the reaction mixture (0.55 mmol/h) to minimize its decomposition under acidic conditions.[7] Upon optimization of reaction parameters, we were then delighted to observe formation of the product *described as* **3** as a single diastereomer in 68% yield using zeolite HY-360 as catalyst. No reaction took place in the absence of the catalyst, and lower yields were achieved increasing the pace of epoxide addition. The product is relatively sensitive to moisture, slowly decomposing to a mixture of starting ketone and *trans*-1,2-cyclohexandiol. A comparable selectivity toward the product (62%) was achieved using BF_3 etherate as catalyst.[5]

Scheme 3. 1,4- vs 1,2-Addition in the Reaction of Epoxide 2a with α,β-Unsaturated Ketone 1a



The heterocycle that we synthesized reproduced all the spectroscopic data reported for dioxepine **3** (^{1}H and ^{13}C NMR, IR, and MS; Figure 1 presents relevant captions of key ^{1}H and ^{13}C NMR resonances). We were, however, puzzled by the attribution of the surprisingly large coupling constant of 15.9 Hz observed in the ^{1}H NMR to the interaction between the benzylic and vinylic protons of **3** (highlighted in purple and

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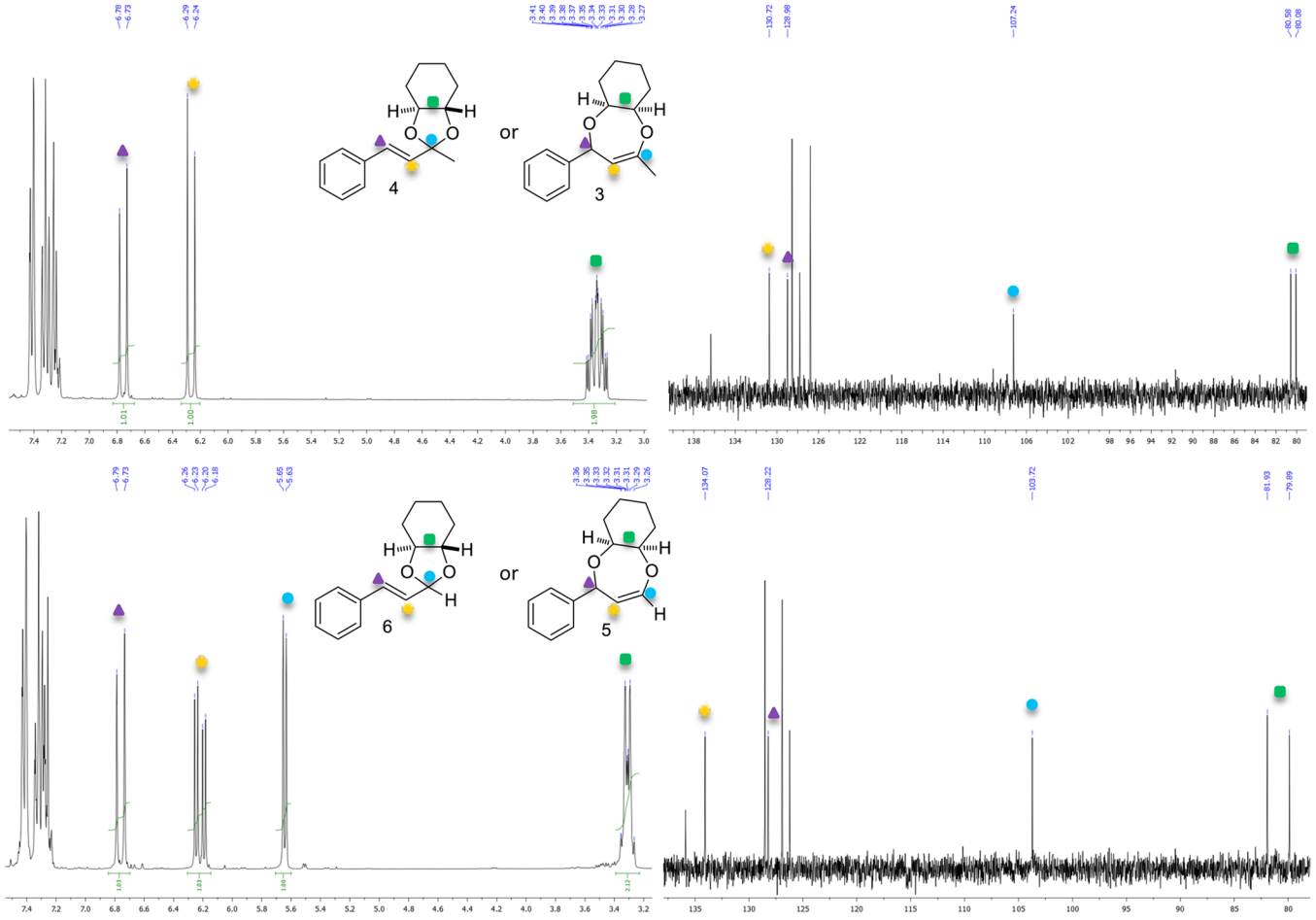

Figure 1. Positions of relevant experimental ^{1}H and ^{13}C resonances of the product between cyclohexene oxide and benzylidenacetone (**3**, **4**, above) and cinnamaldehyde (**5**, **6**, below).

yellow, respectively), and by the downfield chemical shift of the benzylic carbon (129.0 ppm, purple) and the upfield shift of the quaternary enol (107.2 ppm, cyan).

We then decided to model the four possible diastereomers of **3** via DFT and calculate their ^{1}H and ^{13}C NMR spectra to compare them with experimental ones and thus rationalize the outcome of these reactions.[8] Optimizations were performed at the M06 level using the IGLO-III basis set, essentially a triple-ζ one especially designed for NMR simulations, and with chloroform as an implicit solvent via the CPCM approach.

None of the calculated spectra (not shown; see the Supporting Information) matched the experimental ones. Regarding the proton NMR, a large coupling constant (15.9 Hz) observed between the benzylic (purple) and the vinylic (yellow) protons suggests a structure with a relatively small dihedral angle among them. However, in all cases, the calculated coupling constants remain below 10 Hz, in striking contrast with the experimental value of 15.9 Hz. Considering the carbon NMR, the calculated resonances of the sp^3 benzylic carbons of **3** are always considerably below 100 ppm (purple, 81.0 ppm for the diastereomer of Figure 1), while the quaternary sp^2 enol provided in all cases the most downfielded signal of the whole molecule (cyan, 174.9 ppm for the diastereomer of Figure 1).

We then considered the structure of acetal **4**, which could, in principle, form in acidic conditions between the epoxide and the carbonyl group of the α,β-unsaturated partner, leaving the C−C double bond untouched.[9] In this case, a clean correlation between calculated and experimental NMR spectra immediately appeared. The *trans* relation between vinylic protons of the styryl fragment (purple and yellow) evenly matched the experimentally measured large coupling constant among them (calculated J = 17.0 Hz). In **4**, the calculated resonance of the benzylidenic carbon appears in the range expected for sp^2-hybridized species (purple in Figure 1, calculated resonance of 139.1 ppm) and the quaternary carbon provides a signal (107.2 ppm) in the region expected for acetals (cyan, calculated shift of 116.3 ppm).

Besides these spectroscopic features, acetal **4** is thermodynamically more stable than dioxepine **3** by 6.9 kcal/mol in ΔG.

Try as we might, efforts to crystallize these oily products at low temperature to perform X-ray diffraction proved fruitless. As the originally published method reported that unsaturated aldehydes too could be efficient substrates, we decided to perform the reaction with cinnamaldehyde and cyclohexene oxide to determine the actual structure of the heterocyclic product (Scheme 4). If dioxepine **5** forms, it should provide a *cis*-vinylic coupling constant in the ^{1}H NMR spectrum (red arrow in Scheme 4), and a much smaller, aliphatic J should appear in the case of formation of **6** (blue arrow). Gratifingly, by performing the reaction with HY-360 zeolite as catalyst, the heterocyclic product can be retrieved in 84% yield. A similar result, 77%, was achieved with BF_3 etherate as homogeneous catalyst. The observed positions of relevant NMR resonances

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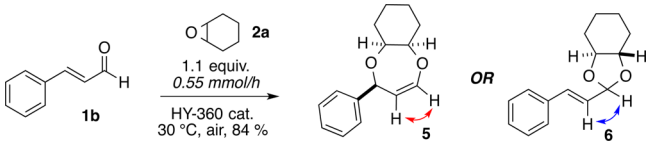
Scheme 4. 1,4- vs 1,2-Addition in the Reaction of Epoxide 2a with Cinnamaldehyde 1b with Colored Arrows Highlighting Key Difference in Their ^{1}H NMR Couplings



are presented in the lower part of Figure 1. Expectedly, the quaternary carbon of **4** has been replaced by a C−H group and this hydrogen (highlighted in cyan) couples with the vinylic proton (highlighted in yellow). The experimental coupling constant is 6.3 Hz. This is in perfect agreement with the structure of acetal **6**, whereas it could not match that of the desired dioxepine **5**. All the other resonances parallel those presented above for acetal **4**.

To exclude that the outcome of these reactions was dictated by the use of a cyclic epoxide, we replaced it with isobutene oxide. The reaction was less efficient with our heterogeneous catalyst (26% yield) than with a homogeneous Lewis acid (65% with BF_3 etherate). Nonetheless, the product (**7**; see the Experimental Section) displayed the same NMR features discussed above for its peers. The reaction of an α,β-unsaturated ketone with styrene or dodecene oxide provided the same reactivity (**8** and **9**, 29% and 40% yield, respectively). NMR resonances consistent with the structure of vinyl acetals were similarly observed reacting **2a** with either 4-chloro- and 4-methoxybenzylidene acetone (**10** and **11**, 83% and 12% yield, respectively) or aliphatic β-ionone (**12**, 55% yield).

On the basis of all of these spectroscopic and computational data, we thus propose to reassign the structure of these heterocyclic molecules as vinyl acetals rather than 1,4-dioxepines. The reaction of α,β-unsaturated carbonyls with epoxides in the presence of an acid catalyst would not provide the product of a formal (4 + 3) cycloaddition but leaves instead conjugated C−C double bonds untouched.

EXPERIMENTAL SECTION

General Procedure. To a round-bottom flask containing 200 mg of zeolite HY-360 was added a solution of the α,β-unsaturated carbonyl compound (3 mmol) in dichloromethane (5 mL), and the resulting mixture was stirred at 30 °C. A solution of the epoxide (3.3 mmol, 1.1 equiv.) in dichloromethane (5 mL) was then slowly added during 6 h via syringe pump (0.55 mmol/h). Upon completion of the addition, the mixture was maintained under stirring for another 2 h. The crude reaction mixture was then filtered, concentrated under reduced pressure, and eventually purified by flash column chromatography on silica gel (1:10 ethyl acetate:hexane).

*2-Methyl-(E)-2-styrylhexahydrobenzo[d][1,3]dioxole (**4**).* Pale yellow oil; R_f = 0.36; yield: 68%, 498 mg; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.41 (2H, d, J = 7.1 Hz, H13), 7.32 (2H, t, J = 7.1 Hz, H14), 7.23 (1H, t, J = 7.1 Hz, H15), 6.76 (1H, d, J = 15.9 Hz, H11), 6.27 (1H, d, J = 15.9 Hz, H10), 3.38 (1H, ddd, J = 9.9, 8.8, 3.7 Hz, H4), 3.30 (1H, ddd, J = 9.9, 8.8, 3.7 Hz, H5), 2.15 (2H, t, J = 9.8 Hz, H6), 1.82 (2H, d, J = 9.7 Hz, H9), 1.59 (3H, s, CH_3), 1.49 (2H, m, H7), 1.29 (2H, m, H8); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 136.3 (C12), 130.7 (C10), 129.0 (C11), 128.5 (C14), 127.8 (C15), 126.8 (C13), 107.2 (C2), 80.6 (C4), 80.1 (C5), 28.9 (C6), 28.7 (C7), 26.2 (CH_3), 23.7 (C8, C9); IR (neat): 2953, 2795, 1502, 1496, 1398, 1267, 1188, 1123, 1078, 984, 839, 758, 689, 650 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{16}H_{21}O_2$ [M + H]$^+$, 245.1536; found: 245.1542.

*(E)-2-Styrylhexahydrobenzo[d][1,3]dioxole (**6**).* Pale yellow oil; R_f = 0.31; yield: 84%, 580 mg; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.42 (2H, d, J = 8.3 Hz, H13), 7.30 (3H, m, H14, H15), 6.75 (1H, d, J = 15.9 Hz, H11), 6.22 (1H, dd, J = 15.9, 6.3 Hz, H10), 5.64 (1H, d, J = 6.3 Hz, H2), 3.32 (2H, m, H4, H5), 2.19 (2H, m, H6), 1.84 (2H, d, J = 8.9 Hz, H9), 1.51 (2H, m, H7), 1.31 (2H, m, H8); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 135.9 (C12), 134.1 (C10), 128.5 (C14), 128.2 (C15), 126.9 (C13), 126.2 (C11), 103.7 (C2), 81.9 (C4), 79.9 (C5), 28.9 (C6), 28.7 (C9), 23.74 (C7), 23.70 (C8); IR (neat): 2932, 2863, 1448, 1397, 1380, 1278, 1205, 1127, 1080, 1048, 920, 870, 758, 697 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{15}H_{19}O_2$ [M + H]$^+$, 231.1380; found: 231.1373.

*2,4,4-Trimethyl-(E)-2-styryl-1,3-dioxolane (**7**).* Pale yellow oil; R_f = 0.46; yield: 26%, 159 mg; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.40 (2H, d, J = 7.2 Hz, H9), 7.32 (2H, t, J = 7.4 Hz, H10), 7.25 (1H, t, J = 7.2 Hz, H11), 6.72 (1H, d, J = 16.0 Hz, H7), 6.21 (1H, d, J = 16.0 Hz, H6), 3.78 (1H, d, J = 8.1 Hz, H4), 3.69 (1H, d, J = 8.1 Hz, H4), 1.56 (3H, s, CH_3(C2)), 1.35 (3H, s, CH_3(C5)), 1.34 (3H, s, CH_3(C5)); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 136.4 (C8), 131.4 (C6), 129.2 (C7), 128.6 (C10), 127.8 (C11), 126.7 (C9), 108.2 (C2), 79.6 (C5), 75.2 (C4), 27.5 (CH_3(C5)), 27.0 (CH_3(C5)), 26.0 (CH_3(C2)); IR (neat): 2948, 2823, 1497, 1481, 1384, 1263, 1198, 1121, 1077, 997, 823, 763, 674, 643 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{14}H_{19}O_2$ [M + H]$^+$, 219.1380; found: 219.1385.

*(E)-2-(4-Chlorostyryl)-2-methyl-4-phenyl-1,3-dioxolane (**8**).* Colorless oil; R_f = 0.34; yield: 29%, 262 mg; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.39−7.24 (9H, m, Ar−H), 6.76 (1H, d, J = 16.1 Hz, H11), 6.34 (1H, d, J = 16.1 Hz, H10), 5.13 (1H, dd, J = 8.9, 5.9 Hz, H4), 4.36 (1H, dd, J = 8.9, 5.9 Hz, H4), 3.74 (1H, t, H5), 1.65 (3H, s, CH_3(C2)); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.1 (C6), 134.8 (C15), 133.6 (C12), 131.2 (C10), 128.8 (C11), 128.6 (C14), 128.2 (C13), 128.0 (C8), 126.6 (C9), 126.4 (C7), 108.8 (C2), 78.7 (C5), 71.8 (C4), 25.8 (CH_3(C2)); IR (neat): 2941, 2937, 2811, 1768, 1729, 1505, 1483, 1386, 1260, 1199, 1111, 1071, 995, 819, 760, 677 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{18}H_{17}O_2ClNa$ [M + Na]$^+$, 323.0809; found: 323.0803.

*4-Decyl-2-methyl-2-(E)-styryl-1,3-dioxolane (**9**).* Colorless oil; two diastereomeric forms denoted as A and B in a 6:4 ratio, R_f = 0.56 and 0.54; combined yield 40%, 397 mg; A: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (2H, d, J = 7.7 Hz, H9), 7.32 (2H, t, J = 7.3 Hz, H10), 7.25 (1H, t, J = 7 Hz, H11), 6.69 (1H, d, J = 15.9 Hz, H7), 6.15 (1H, d, J = 15.9 Hz, H6), 4.09 (1H, m, H5), 4.01 (1H, m, H4), 3.57 (1H, t, J = 6.9 Hz, H4), 1.54 (3H, s, CH_3(C2)), 1.26 (18H, m), 0.88 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 136.3 (C8), 130.3 (C6), 129.3 (C7), 128.5 (C10), 127.8 (C11), 126.7 (C9), 107.6 (C2), 76.1 (C5), 69.6 (C4), 33.36, 31.9, 29.71, 29.65, 29.60, 29.56, 29.52, 29.3 (CH_2 decyl chain), 26.0 (CH_3(decyl)), 25.7 (CH_3(C2)). B: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (2H, d, J = 7.2 Hz, H9), 7.32 (2H, t, J = 7.5 Hz, H10), 7.24 (1H, t, J = 7.2 Hz, H11), 6.72 (1H, d, J = 16.0 Hz, H7), 6.23 (1H, d, J = 16.0 Hz, H6), 4.12 (2H, m, H4, H5), 3.51 (1H, t, J = 7.4 Hz, H4), 1.54 (3H, s, CH_3(C2)), 1.26 (18H, m), 0.88 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 136.4 (C8), 131.2 (C6), 129.4 (C7), 128.6 (C10), 127.8 (C11), 126.8 (C9), 107.7 (C2), 76.7 (C5), 69.9 (C4), 33.3, 31.9, 29.71, 29.66, 29.60, 29.56, 29.53, 29.3 (CH_2 decyl chain), 26.0 (CH_3(decyl)), 25.7 (CH_3(C2)); IR (neat): 2940, 2815, 1502, 1485, 1383, 1264, 1194, 1113, 1069, 999, 824, 763, 676 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{22}H_{37}O_2$ [M + H]$^+$, 331.2632; found: 331.2636.

*(E)-2-(4-Chlorostyryl)-2-methylhexahydrobenzo[d][1,3]dioxole (**10**).* Pale yellow oil; R_f = 0.33; yield 83%, 694 mg; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ 7.36 (2H, d, J = 8.5 Hz, H13), 7.30 (2H, d, J = 8.5 Hz, H14), 6.73 (1H, d, J = 15.9 Hz, H11), 6.26 (1H, d, J = 15.9 Hz, H10), 3.39 (1H, ddd, J = 12.4, 8.9, 3.8 Hz, H4), 3.31 (1H, ddd, J = 12.4, 8.9, 3.8 Hz, H5), 2.157 (2H, dd, J = 12.7, 9.5 Hz, H6), 1.84 (2H, d, J = 9.1 Hz, H9), 1.60 (3H, s, CH_3(C2)), 1.49 (2H, m, H7), 1.32 (2H, m, H8); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 134.9 (C15), 133.4 (C10), 131.4 (C12), 128.7 (C11), 128.0 (C13), 127.8 (C14), 107.1 (C2), 80.6 (C4), 80.2 (C5), 28.9 (C6), 28.7 (C7), 26.1 (CH_3), 23.7 (C8, C9); IR (neat): 2943, 2808, 1774, 1731, 1502, 1488, 1392, 1264, 1192, 1113, 1073, 1000, 822, 764, 678 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{16}H_{20}O_2Cl$ [M + H]$^+$, 279.1146; found: 279.1152.

*(E)-2-(4-Methoxystyryl)-2-methylhexahydrobenzo[d][1,3]dioxole (**11**).* Pale yellow oil; R_f = 0.26; yield 12%, 99 mg; ^{1}H NMR (300.1

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MHz, $CDCl_3$): δ 7.35 (2H, d, J = 8.7 Hz, H13), 6.85 (2H, d, J = 8.7 Hz, H14), 6.70 (1H, d, J = 15.9 Hz, H11), 6.13 (1H, d, J = 15.9 Hz, H10), 3.80 (3H, s, OCH_3), 3.37 (1H, ddd, J = 12.5, 8.8, 3.7 Hz, H4), 3.29 (1H, ddd, J = 12.5, 8.8, 3.7 Hz, H5), 2.15 (2H, t, J = 9.7 Hz, H6), 1.81 (2H, d, J = 9.8 Hz, H9), 1.58 (3H, s, CH_3(C2)), 1.48 (2H, m, H7), 1.29 (2H, m, H8); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 159.4 (C15), 129.1 (C10), 128.6 (C12), 128.5 (C11), 128.0 (C14), 113.9 (C13), 107.4 (C2), 80.5 (C4), 80.0 (C5), 55.3 (OCH_3), 28.9 (C6), 28.7 (C7), 26.3 (CH_3(C2)), 23.8 (C8, C9); IR (neat): 2940, 2818, 1611, 1589, 1512, 1491, 1397, 1265, 1189, 1115, 1074, 992, 825, 761, 673 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{17}H_{23}O_3$ [M + H]$^+$, 275.1642; found: 275.1639.

*(E)-2-Methyl-2-(2-(2,6,6-trimethylcyclohex-1-en-1-yl)vinyl)hexahydrobenzo[d][1,3]dioxole (**12**).* Colorless oil; R_f = 0.40; yield: 55%, 479 mg; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 6.26 (1H, d, J = 16 Hz, H10), 5.49 (1H, d, J = 16 Hz, H11), 3.33 (1H, ddd, J = 12.5, 8.7, 3.7 Hz, H4), 3.27 (1H, ddd, J = 12.5, 8.8, 3.7 Hz, H5), 2.14 (2H, t, J = 9.5 Hz, H6), 1.97 (2H, t, J = 6.1 Hz, H14), 1.81 (2H, dd, J = 9.0 Hz, H9), 1.67 (3H, s, CH_3(C2)), 1.60 (2H, m, H15), 1.53 (3H, s, CH_3(C13)), 1.45 (4H, m, H7, H16), 1.29 (2H, m, H8), 0.99 (3H, s, CH_3(C17)), 0.98 (3H, s, CH_3(C17)); ^{13}C NMR (100.5 MHz, $CDCl_3$): δ 136.5 (C12), 134.7 (C10), 128.6 (C13), 127.2 (C11), 107.4 (C2), 80.6 (C4), 79.9 (C5), 39.4 (C14), 33.9 (C17), 32.6 (C15), 29.1 (C6), 28.8 (C16), 28.7 (C7), 28.7 (CH_3(C13)), 26.2 (CH_3(C2)), 23.8 (C8), 23.8 (C9), 21.3 (CH_3(C17)), 19.3 (CH_3(C17)); IR (neat): 2822, 1609, 1582, 1519, 1487, 1402, 1263, 1193, 1110, 1079, 989, 831, 744, 680 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{19}H_{31}O_2$ [M + H]$^+$, 291.2317; found: 291.2312.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, computational data, and copy of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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