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Total Synthesis of (+)-Cymbodiacetal: A Re-evaluation of the Biomimetic Route

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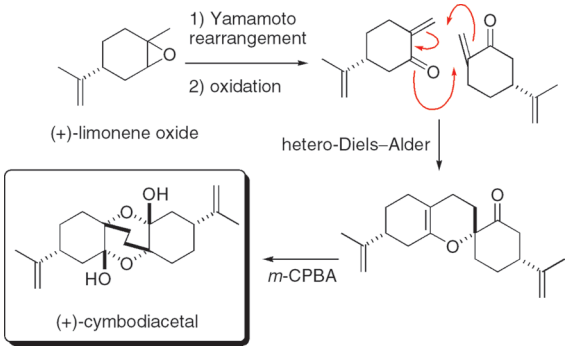

A total synthesis of (+)-cymbodiacetal (**1**) has been completed from (*R*)-(+)-limonene oxide using a hetero-Diels−Alder cycloaddition as a key step. The key Diels−Alder cycloaddition proceeds with *endo*-selectivity (2:1, *endo*/*exo*) in quantitative yield, and the two diastereomeric spirochroman products are isolable, stable products. Furthermore, the *exo*- and the *endo*-hetero-Diels−Alder cycloaddition products (**2** and **7**) can be oxidized with *m*-CPBA to produce (+)-cymbodiacetal (**1**) and the C_2-symmetric bis-hemiacetal structure **8**, respectively. The isomeric hemiacetal **9** is produced in both oxidation reactions. The structures of (+)-cymbodiacetal (**1**), its C_2-symmetric diastereoisomer **8**, and the isomeric hemiacetal **9** were confirmed using X-ray crystallography.

Introduction

The structurally intriguing natural product (+)-cymbodiacetal (**1**) was isolated in 1987 by Dev from the aerial parts of flowering wild *Cymbopogon martinii*.[1] Its structure was elucidated using a combination of spectroscopic (^{1}H, ^{13}C NMR, IR, MS) and X-ray crystallographic techniques, and the fortuitous fact that **1** crystallized as a 1:1 solvate with $CDCl_3$ enabled the absolute stereochemistry to be determined from the X-ray data due to the presence of the heavy atoms. However and rather peculiarly, the representation derived from the X-ray analysis and the structure actually drawn for **1** are presented as enantiomers of each other in Figure 1 of the original isolation paper. Unfortunately, and despite what is stated in the Experimental Section of the isolation paper, the original X-ray data is not available from the Cambridge Crystallographic database so it is not possible to clarify this obvious discrepancy. Circumstantial evidence for the absolute stereochemistry of **1** comes from the fact that the monoterpene (*R*)-(+)-limonene (**4**) was also isolated as a major component of the essential oil from *Cymbopogon martinii*,[1] and as this material appears to be an obvious biosynthetic precursor to **1** (Figure 1), it therefore follows that C2 and C7 of **1** would also share (+)-limonene's *R*-configuration. This stereochemical hypothesis was later shown to be correct when in 2004 Kamat[2] reported a biomimetic total synthesis of **1** starting from (+)-limonene oxide, thus confirming the absolute stereochemistry of **1** to be as shown below (Figure 1).

The spirochroman **2**, which is a key intermediate in both the proposed biosynthesis and Kamat's total synthesis, is the product of an *exo*-hetero-Diels−Alder dimerization of the limonene-derived exocyclic enone **3**.[3] Kamat found enone **3**

(1) Bottini, A. T.; Dev, V.; Garfagnoli, D. J.; Hope, H.; Joshi, P.; Lohani, H.; Mathela, C. S.; Nelson, T. E. *Phytochemistry* **1987**, *26*, 2301.

(2) D'Souza, A. M.; Paknikar, S. K.; Dev, V.; Beauchamp, P. S.; Kamat, S. P. *J. Nat. Prod.* **2004**, *67*, 700.

(3) For other spirochroman-containing natural products, see: (a) Zhang, Y.; Lu, Y.; Mao, L.; Proksch, P.; Lin, W. *Org. Lett.* **2005**, *7*, 3037. (b) Inouye, Y.; Sugo, Y.; Kusumi, T.; Fusetani, N. *Chem. Lett.* **1994**, 419. (c) Carreiras, M. C.; Rodriguez, B.; Lopez-Garcia, R. E.; Rabanal, R. M. *Phytochemistry* **1987**, *26*, 3351. (d) Adesomoju, A. A.; Okogun, J. I. *J. Nat. Prod.* **1984**, *47*, 308. (e) Takemoto, T.; Nakajima, T. *Yakugaku Zasshi* **1955**, *75*, 1036.

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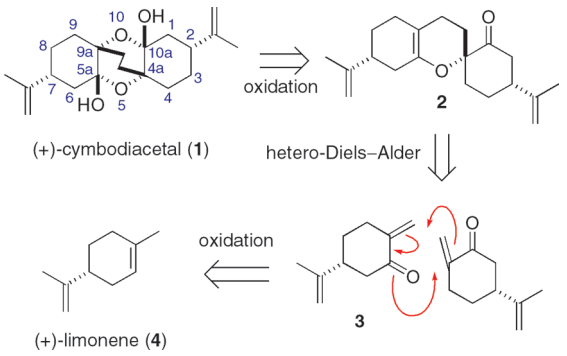
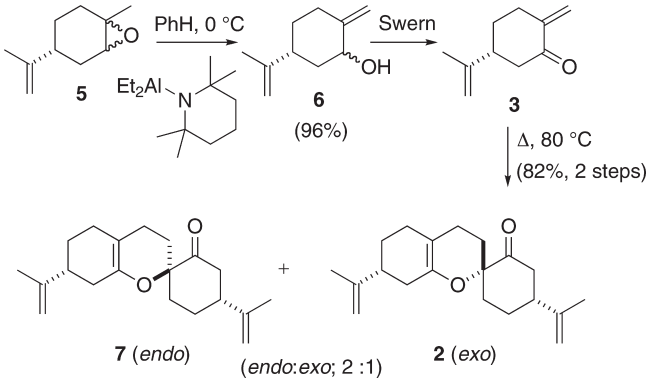


FIGURE 1. Biosynthetic hypothesis for the formation of (+)-cymbodiacetal (**1**).

SCHEME 1. Synthesis of Spirochromans 2 and 7 via Hetero-Diels−Alder Cycloaddition



to be unstable and reported that it dimerized and oxidized to give **1** directly upon exposure to air and silica gel column chromatography. While this reported synthesis appears to be beautifully simple, and supports the likely biosynthetic origin of the natural product, several of its features caught our attention, as they appeared to contradict results obtained within our own laboratory.[4] We now report a full account of our studies on the synthesis of (+)-cymbodiacetal (**1**), which have resulted in a total synthesis of the natural product **1**, along with two other isomeric structures, and we have been able to obtain our own X-ray structure of **1** thus clarifying the original uncertainty surrounding the absolute stereochemistry.

Results and Discussion

Our synthesis began by converting (*R*)-(+)-limonene oxide **5** into the corresponding allylic alcohol **6** in 96% yield using Yamamoto's conditions.[5] The allylic alcohol **6** was then cleanly oxidized to the enone **3** in good yield (80−90% crude yield) under Swern conditions[6] (Scheme 1). It was at this point in our studies that we started to observe differences between our results and those described by Kamat.[2] First, the enone **3** was found to be relatively stable in its crude form, and a full set of spectroscopic data was obtained for this compound.[7] While the enone **3** appeared to account for >90% of the crude material, the yield of pure **3** was only 62% after chromatography. In order to account for the missing mass balance, the remaining fractions from the column were collected, and we were pleased to see that the spirochroman **2** and its diastereoisomer **7** (ratio 1:2) could also be isolated in a combined 20% yield. As the stereochemistry of **2** and **7** could not be determined directly, their stereochemistry was assigned at a later stage by converting **2** into the natural product **1** (see below). As the compounds **2** and **7** were obviously produced via the hetero-Diels−Alder dimerization of the enone **3** during purification, the separated pure sample of **3** was heated at 80 °C for 8 h in order to convert all the enone **3** into **2** and **7**. Pleasingly, the hetero-Diels−Alder dimerization proved to be very efficient, and the desired spirochromans **7** and **2** (2:1 ratio) were isolated in quantitative yield.[8]

Although Kamat had previously described the minor *exo*-Diels−Alder product **2**, it is somewhat surprising that major *endo*-Diels−Alder product **7** hadn't been observed in their work.[9] Compound **7** is clearly the major product of hetero-Diels−Alder dimerization of **3** under their reported conditions (rt, 7 days), and we checked this independently. In addition, and contrary to the report of Kamat, we found the *exo*-Diels−Alder product **2** to be a stable, easy to handle oil, which could be purified easily using silica gel column chromatography. Indeed, Kamat states that **2** "was difficult to obtain in pure form" and that it was oxidized in air, in the presence of "diffused daylight", to afford (+)-cymbodiacetal (**1**) after column chromatography. Once again, we independently checked this claim by exposing a sample of pure **2** to air and sunlight over an extended period (15 days), but no evidence of oxidation at all could be found under these conditions, and **2** was recovered unchanged after this time. For the sake of completeness, we also exposed the *endo*-isomer **7** to the same air/sunlight conditions and once again found that no oxidation reaction took place.

The stark difference in reactivity (stability) of **2** observed by Kamat and by us is quite difficult to explain, but one possibility could stem from the method used to prepare the enone **3**. In our work, a Swern oxidation was used to obtain **3**, whereas Kamat used a PCC oxidation. In our hands, **3** was relatively easy to handle, whereas Kamat found it difficult to handle. It is possible, therefore, that chromium-based impurities (from PCC) were contaminating Kamat's samples of **3** and **2**, and it was these impurities that were responsible for the observed instability of **3** and for the oxidation of **2** to **1** upon standing in air/sunlight.[10,11] We have subsequently

(4) For the only other previous work on the synthesis of (+)-cymbodiacetal, see: Barrero, A. F.; Herrador, M. M.; Quilez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Dieguez, H. R.; Sanchez, E. M. *J. Org. Chem.* **2007**, *72*, 2988.

(5) Yasuda, A.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1705.

(6) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(7) However, upon standing for prolonged periods, the enone **3** completely dimerizes to form the spirochromans **2** and **7**.

(8) For background information regarding this type of hetero-Diels−Alder cycloaddition, see: (a) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (b) Colonge, J.; Descotes, G. α,β-Unsaturated Carbonyl Compounds as Dienes. In *Organic Chemistry*; Hamer, J., Ed.; Academic Press: New York, 1967; Vol. 8, pp 217−253.

(9) (a) Hetero-Diels−Alder cycloadditions of this type are reported to be *endo*-selective: Hosoyama, H.; Shigemori, H.; In, Y.; Ishida, T.; Kobayashi, J. *Tetrahedron Lett.* **1998**, *39*, 2159. (b) For a description of the Alder *endo*-rule, see: Alder, K.; Stein, G. *Angew. Chem.* **1937**, *50*, 510.

(10) It has been reported that PCC can perform epoxidations (see ref 11). It is therefore possible that **2** is being oxidized in situ to produce **14** (or closely related species), which then reacts further under the acidic reaction conditions to produce **1**.

(11) (a) Gamba, D.; Pisoni, D. S.; da Costa, J. S.; Petzhold, C. L.; Borges, A. C. A.; Ceschi, M. A. *J. Braz. Chem. Soc.* **2008**, *19*, 1270. (b) Sundararaman, P.; Herz, W. *J. Org. Chem.* **1977**, *42*, 813.

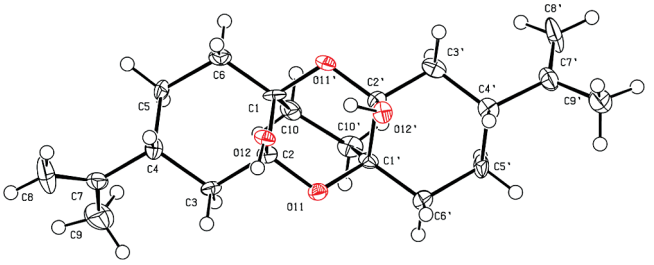
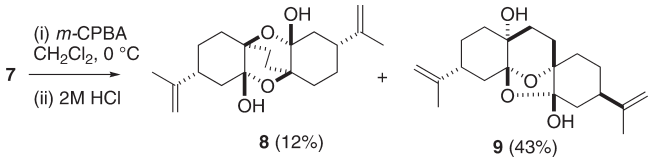


FIGURE 2. X-ray crystal structure of **8**.

SCHEME 2. Oxidation of *endo*-Hetero-Diels–Alder Product 7



repeated Kamat's published synthetic procedures, but unfortunately, their synthesis of **1** could not be reproduced. We therefore decided to perform our own oxidation studies on **2**, and its diastereoisomer **7**, in order to develop an independent and reliable synthesis of **1**.

As mentioned above, the relative stereochemistries of **2** and **7** could only be determined retrospectively by converting one of them into the natural product **1**, so our oxidation studies began on the major diastereomer (which was subsequently shown to be the *endo*-isomer **7**) that resulted from the hetero-Diels–Alder dimerization of **3**. Thus, treatment of **7** with *m*-CPBA resulted in rapid oxidation of the electron-rich enol-ether to provide a mixture of unstable products that were immediately treated with 2 M HCl.[12] Workup and subsequent purification by column chromatography led to the isolation of two new oxidation products, neither of which had spectroscopic data that matched that reported for (+)-cymbodiacetal (**1**) (Scheme 2).

The ^{13}C NMR spectrum of the minor compound **8** (12% yield) showed only 10 resonances, and the proposed C_2-symmetric structure was confirmed via X-ray crystallography (Figure 2).[13] The high-resolution mass spectrum of product **9** confirmed that it was an isomer of **8**, and the ^{1}H and ^{13}C NMR data showed that it did not have C_2-symmetry. X-ray crystallography was once again used to confirm the overall structural assignment (Figure 3).[13]

It was very clear from the X-ray structure obtained for **8** that the major hetero-Diels–Alder dimerization product **7** must have formed via an *endo*-cycloaddition pathway and that oxidation/cyclization of **7** does not lead to (+)-cymbodiacetal (**1**). The formation of **8** and **9** from **7** can be explained by invoking epoxidation of the enol ether to give the diastereomeric epoxides **10** and **11** (Scheme 3). The epoxide **10** produced on the minor reaction pathway then opens in the

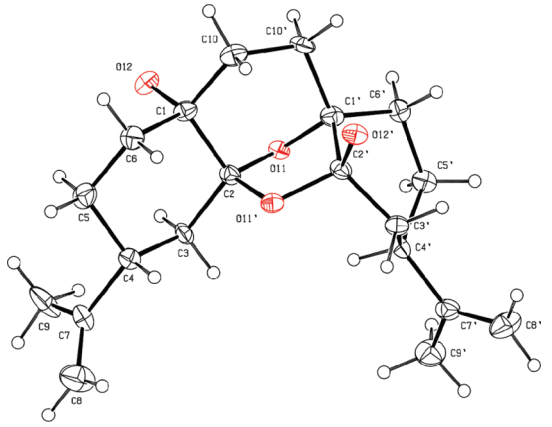
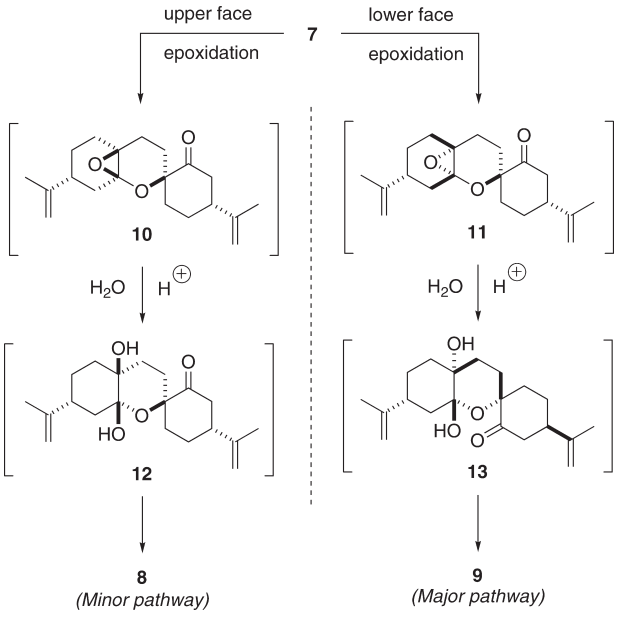


FIGURE 3. X-ray crystal structure of **9**.

SCHEME 3. Suggested Reaction Pathways for the Formation of 8 and 9



presence of water (and acid) to give the diol **12**. Cyclization of one of the two hydroxyls onto the ketone then forms the observed bis-hemiacetal **8**, which is a diastereoisomer of (+)-cymbodiacetal (**1**). Likewise, the major epoxide **11** opens to give the diol **13**, which after hemiacetalization produces the observed major product **9** (Scheme 3).

Having unambiguously defined the stereochemistry of the two hetero-Diels–Alder dimerization products **2** and **7**, we were now in a position to complete a total synthesis of (+)-cymbodiacetal (**1**) by conducting oxidation/cyclization studies on the *exo*-cycloaddition product **2**. Thus, **2** was exposed to *m*-CPBA in CH_2Cl_2 (Scheme 4), and once TLC analysis showed that all starting material had been consumed, the reaction was quenched and NMR spectra were recorded for the crude reaction mixture. As the crude mixture was not soluble in $CDCl_3$, the sample was dissolved in CD_3OD, and the NMR data were collected in that solvent. We were pleased to see that a major new product had been formed, but it was obviously not the epoxide **14** as it appeared to possess C_2-symmetry, similar to the natural product **1**. Indeed,

(12) Catalysis of this transformation with either 2 M HCl (THF/H_2O) or *p*TSA (THF/H_2O) leads to identical results, and the two methods can be used interchangeably.

(13) The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre. CCDC 790825 contains the supplementary crystallographic data for **1**, CCDC 790826 contains the supplementary crystallographic data for **8**, CCDC 790827 contains the supplementary crystallographic data for **9**, and CCDC 790828 contains the supplementary crystallographic data for **16**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_ request/cif.

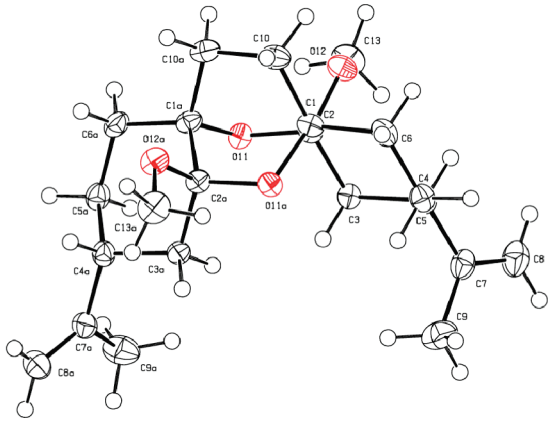
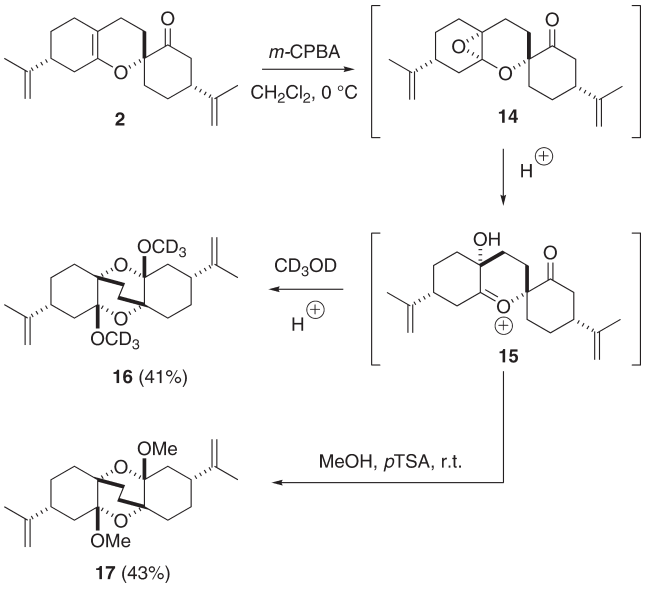


FIGURE 4. X-ray crystal structure of C_2-symmetric bisacetal **16**.

SCHEME 4. Preliminary Oxidation and Acetalization Studies on Spirochroman 2



a closer inspection of the data revealed a striking similarity between the new product **16** and (+)-cymbodiacetal (**1**). Subsequent purification of the crude reaction mixture by column chromatography allowed the major product **16** to be isolated in 41% yield as a crystalline solid. A single-crystal X-ray structure was determined for **16** (Figure 4),[13] and to our surprise, it contained two OCD_3 groups, the presence of which we had missed due to the fact that only ^1H and ^{13}C NMR spectroscopy had been used to analyze the crude material. Subsequent ^2H NMR analysis of the purified material showed a peak at 3.24 ppm for the CD_3O moieties, and high-resolution mass spectrometry also clearly showed their presence.

The formation of **16** is best explained by epoxidation of **2** from the lower face (as drawn) to give the epoxide **14** as a transient intermediate. Upon workup and exposure to CD_3OD in the presence of acid (presumably residual chlorobenzoic acid), the epoxide **14** then forms the oxocarbenium ion **15**, which is then trapped by CD_3OD. Closure of the second acetal under the same conditions then gives **16** as the major product. In order to confirm this hypothesis, we deliberately attempted to prepare the bis-acetal **17** from **2** by

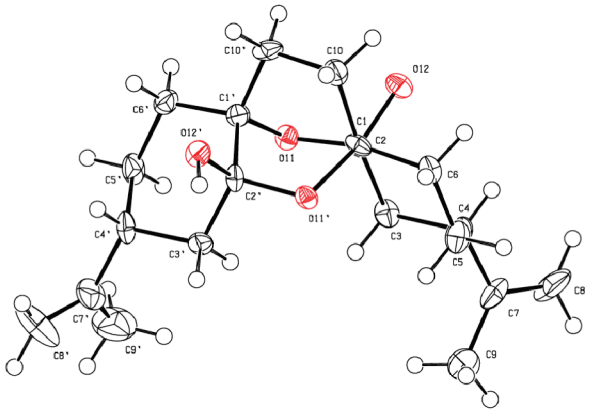
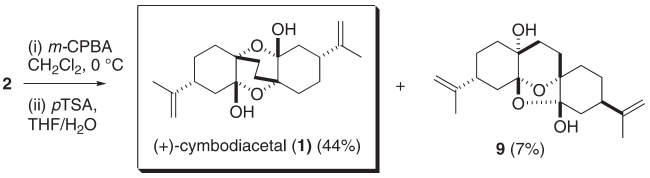


FIGURE 5. X-ray crystal structure of (+)-cymbodiacetal (**1**).

SCHEME 5. Synthesis of (+)-Cymbodiacetal (1) by Oxidation of 2



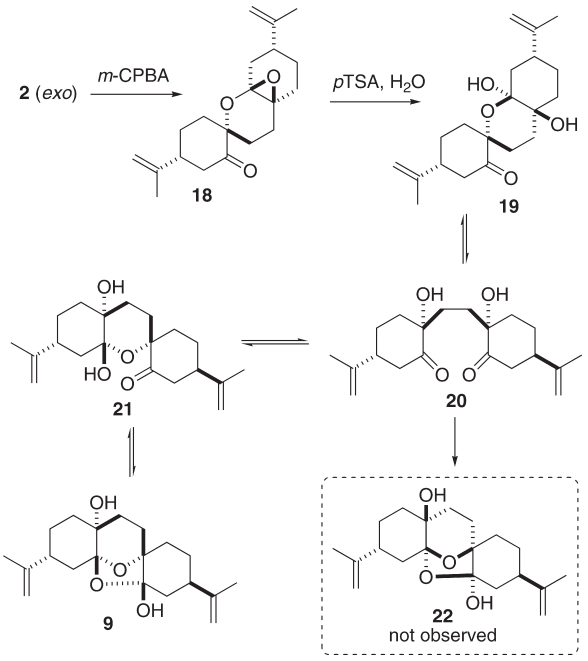
first treating with *m*-CPBA to obtain the crude epoxide **14**. This material was then reacted immediately with MeOH in the presence of *p*TSA (10 mol %) to afford **17** in 43% yield (Scheme 4).

Guided by these results, we were able to complete a total synthesis of (+)-cymbodiacetal (**1**) by first treating **2** with *m*-CPBA to produce **14**. A THF solution of the crude material was then reacted with water in the presence of *p*TSA[12] (10 mol %), and to our pleasure, (+)-cymbodiacetal (**1**) was produced as a major product (44%) from the two-step sequence (Scheme 5).

Our synthetic sample of **1** showed identical spectroscopic data[1] to that reported for the natural product, and in addition we were able to obtain our own X-ray crystal structure of the 1:1 solvate of **1** with $CDCl_3$ (Figure 5),[13] which unambiguously confirmed its absolute configuration. In addition to the formation of **1**, the acetal **9** was also formed as a minor product (7%) in the reaction. We were initially surprised at this finding, as we had previously seen **9** as the major product from the *m*-CPBA oxidation of the *endo*-hetero-Diels−Alder product **7** (Scheme 2). The formation of **9** from the *exo*-hetero-Diels−Alder product **2** can be accounted for by the following minor reaction pathway shown in Scheme 6. Thus, oxidation of **2** with *m*-CPBA on the upper face of the enol ether first produces the epoxide **18**, which upon opening with water produces the hemiacetal **19**. The hemiacetal **19** then rearranges, via the dihydroxy dione **20**, to produce the new hemiacetal **21** and a second hemiacetal formation then finally affords **9**. It is interesting to note that the isomeric hemiacetal **22**, which could form directly from **19** or indirectly from **20**, was not observed.

In conclusion, we have successfully completed a total synthesis of (+)-cymbodiacetal (**1**) from (*R*)-(+)-limonene oxide using a hetero-Diels−Alder cycloaddition as a key step. We have shown that the Diels−Alder cycloaddition proceeds with *endo*-selectivity (2:1, *endo*/*exo*) in quantitative

SCHEME 6. Suggested Pathway for the Formation of 9 from Spirochroman 2



yield to provide two stable, isolable isomeric spirochroman products (**7** and **2**), which do not spontaneously oxidize in air and sunlight to form **1**. These findings are clearly contrary to results previously reported in the literature.[2] Furthermore, we have shown that the *exo*- and the *endo*-hetero-Diels–Alder cycloaddition products (**2** and **7**) can be oxidized with *m*-CPBA to produce (+)-cymbodiacetal (**1**) and the C_2-symmetric bis-hemiacetal **8**, respectively. The isomeric hemiacetal **9** is also produced in both oxidation reactions, and all structural and stereochemical assignments have been confirmed via X-ray crystallography.

Experimental Section

(*R*)-2-Methylene-5-(prop-1-en-2-yl)cyclohexanol 6. Freshly distilled tetramethylpiperidine (2.44 mL, 14.5 mmol) was diluted with benzene (20 mL), the resulting solution was cooled to 0 °C, *n*-butyllithium (6.28 mL, 14.5 mmol, 2.30 M solution in hexanes) was then added, and the colorless solution turned yellow. After 30 min of stirring, diethylaluminum chloride (16.6 mL, 16.6 mmol, 1.00 M solution in hexanes) was added, the yellow color disappeared, and a turbid solution formed. After a further 40 min of stirring at 0 °C, the epoxide **5** (1.10 g, 7.23 mmol) was added as a solution in benzene (7 mL). The reaction mixture was stirred for 45 min at 0 °C and then for 2 h at rt. The reaction was quenched with the slow addition of saturated $NaHCO_3$ (20 mL) at 0 °C, extracted with $CHCl_3$ (20 mL × 3), washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography (pentane/Et_2O; 4/1) afforded the product **6** as a 1:1 mixture of diastereoisomers (1.05 g, 96%) as a colorless oil: $[\alpha]^{25}_D$ +54.0 (*c* 0.95 $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 2954, 2929, 2857, 1668, 1457; NMR δ_H (400 MHz, $CDCl_3$, 298 K) 4.95 (1H, s), 4.85 (1H, s), 4.79 (1H, s), 4.77 (1H, s), 4.71 (4H, s), 4.37 (1H, s), 4.15–4.06 (1H, m), 2.60–2.41 (3H, m), 2.26–2.13 (3H, m), 2.11–1.95 (2H, m), 1.89–1.78 (2H, m), 1.73 (6H, s), 1.53–1.43 (1H, m), 1.33–1.18 (3H, m); NMR δ_C (100 MHz, $CDCl_3$, 298 K) 151.3 (C), 149.9 (C), 149.5 (C), 148.7 (C) 109.9 (CH_2), 109.2 (CH_2), 108.9 (CH_2), 103.9 (CH_2), 72.5 (CH), 72.2 (CH), 44.1 (CH), 42.2 (CH_2), 39.0 (CH_2), 38.2 (CH), 33.8 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 30.0 (CH_2), 21.0 (CH_3), 20.8 (CH_3); MS *m*/*z* (ES^+) 175.1089 (M + Na $C_{10}H_{16}NaO$ requires 175.1093). These data are identical to those previously reported.[2]

(*R*)-2-Methylene-5-(prop-1-en-2-yl)cyclohexanone (3) (and Spirochromans 2 and 7). A solution of DMSO (1.86 mL, 26.2 mmol) in CH_2Cl_2 (6 mL) was added dropwise to a stirred and cooled solution of oxalyl chloride (1.11 mL, 13.1 mmol) in CH_2Cl_2 (5 mL) at −78 °C. After 1.5 h, a solution of allylic alcohol **6** (1.00 g, 6.56 mmol) in CH_2Cl_2 (33 mL) was added at −78 °C. After a further 1.5 h, triethylamine (8.20 mL, 59.04 mmol) was added, and the reaction mixture was stirred for 2 h. The reaction mixture was warmed to 0 °C and stirred for 20 min. The reaction was quenched with saturated $NaHCO_3$ (30 mL), diluted with CH_2Cl_2 (20 mL), extracted with CH_2Cl_2 (20 mL × 3), washed with water (50 mL × 2), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography (pentane/Et_2O; 20/1) afforded the spirochroman **2** (65 mg, 7%) as a colorless oil: $[\alpha]^{26}_D$ +59.0 (*c* 1.6 $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3550, 3086, 2925, 2840, 1715, 1644, 1452, 1375, 1305, 1151, 1130, 1070, 982; NMR δ_H (400 MHz, $CDCl_3$, 298 K) 4.76 (2H, br s), 4.73 (1H, app t, J = 1.5 Hz), 4.71 (1H, app t, J = 0.8 Hz), 2.87 (1H, dd, J = 12.3, 11.2 Hz), 2.33 (1H, app tt, J = 12.4, 3.6 Hz), 2.24–2.17 (3H, m), 2.15–2.10 (4H, m), 1.98–1.85 (3H, m), 1.78–1.70 (8H, m), 1.66–1.59 (1H, m), 1.56–1.44 (2H, m), 1.39–1.24 (1H, m); NMR δ_C (100 MHz, $CDCl_3$, 298 K) 212.5 (C), 149.3 (C), 147.5 (C), 144.0 (C), 110.0 (CH_2), 108.8 (CH_2), 105.6 (C), 79.4 (C), 48.6 (CH), 43.5 (CH_2), 41.8 (CH), 39.0 (CH_2), 33.1 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 27.4 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 20.9 (CH_3), 20.4 (CH_3); MS *m*/*z* (ES^+) 301.2150 (M + H $C_{20}H_{29}O_2$ requires 301.2162). Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.94; H, 9.42. These data are in agreement with those previously reported for **2**.[2] Further elution with (pentane/Et_2O; 15/1) afforded the pure enone **3** (610 mg, 62%) as a colorless oil: $[\alpha]^{27}_D$ +71.3 (*c* 1.17 $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 2926, 2839, 1718, 1699, 1644, 1455, 1375, 1151, 1130, 896; NMR δ_H (400 MHz, $CDCl_3$, 298 K) 5.86 (1H, br s), 5.16 (1H, app dd, J = 3.4, 2.1 Hz), 4.80 (1H, app t, J = 1.3 Hz), 4.72 (1H, br s), 2.69 (1H, app tt, J = 8.1, 1.1 Hz), 2.65–2.58 (1H, m), 2.55–2.43 (2H, m), 2.32 (1H, dd, J = 16.6, 5.3 Hz), 2.10–1.92 (1H, m), 1.75 (3H, s), 1.71–1.59 (1H, m); NMR δ_C (100 MHz, $CDCl_3$, 298 K) 201.5 (C), 147.3 (C), 144.5 (C), 120.6 (CH_2), 110.4 (CH_2), 45.7 (CH_2), 42.7 (CH), 31.2 (CH_2), 29.1 (CH_2), 20.8 (CH_3); MS *m*/*z* (ES^+) 301.2157 (2M + H $C_{20}H_{29}O_2$ requires 301.2162). Further elution with (pentane/Et_2O; 10/1) afforded the spirochroman **7** (132 mg, 13%) as a colorless oil: $[\alpha]^{26}_D$ +96.5 (*c* 1.65 $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3532, 3086, 2919, 2839, 1721, 1700, 1644, 1455, 1375, 1305, 1152, 1130, 986; NMR δ_H (400 MHz, $CDCl_3$, 298 K) 4.80 (1H, s), 4.75 (1H, s), 4.72 (2H, s), 2.58–2.40 (3H, m), 2.34–2.21 (2H, m), 2.18–1.93 (5H, m), 1.90–1.82 (2H, m), 1.80–1.70 (10H, m), 1.49–1.23 (2H, m); NMR δ_C (100 MHz, $CDCl_3$, 298 K) 208.4 (C), 149.3 (C), 146.8 (C), 144.7 (C), 110.5 (CH_2), 108.8 (CH_2), 102.3 (C), 81.1 (C), 46.1 (CH), 43.2 (CH_2), 41.5 (CH), 35.3 (CH_2), 34.2 (CH_2), 28.6 (CH_2), 28.1 (CH_2), 27.7 (CH_2), 26.7 (CH_2), 22.4 (CH_2), 21.0 (CH_3), 20.9 (CH_3); MS *m*/*z* (ES^+) 301.2155 (M + H $C_{20}H_{29}O_2$ requires 301.2162). Anal. Calcd for $C_{20}H_{28}O_2$ requires C, 79.96; H, 9.39. Found: C, 79.65; H, 9.40.

(1′*R*,4′*R*,7*R*)-4′,7-Di(prop-1-en-2-yl)-3,4,5,6,7,8-hexahydrospiro-[chromene-2,1′-cyclohexan]-2′-one (2) and (1′*S*,4′*R*,7*R*)-4′,7-Di-(prop-1-en-2-yl)-3,4,5,6,7,8-hexahydrospiro[chromene-2,1′-cyclohexan]-2′-one (7). The enone **3** (234 mg, 1.56 mmol) was heated in a sealed tube at 80 °C for 8 h in an oil bath in the absence of solvent. The ^1H NMR spectrum of the crude reaction mixture confirmed complete consumption of starting material **3**, and the residue was

purified by column chromatography (pentane/Et_2O; 20/1) to afford **2** (77 mg, 33%) and **7** (154 mg, 66%) as colorless oils, whose data were identical to that previously obtained in this work.

Synthesis of 8 and 9. Spirochroman **7** (55 mg, 0.18 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C, and then *m*-CPBA (40 mg of 70 wt %, 0.16 mmol) was added in one portion and stirred at 0 °C for 45 min. The reaction was quenched with saturated $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product as a colorless oil. The crude product was dissolved in THF (1.00 mL), and 2 M HCl (1.00 mL) was then added. The resulting solution was stirred for a further 1 h at rt. The reaction was quenched with saturated $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography (pentane/Et_2O; 10/1−4/1−2/1) afforded the product **8** (7 mg, 12%) and **9** (26 mg, 43%) both as white crystalline solids.

Data for 8: mp 215−218 °C; $[\alpha]^{25}_D$ +39.1 (*c* 0.40 $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3574, 2944, 2359, 1644, 1456, 1165, 989, 908; NMR δ_H (500 MHz, $CDCl_3$, 298 K) 4.73 (1H, s), 4.69 (1H, s), 2.34 (1H, app tt, J = 12.6, 3.7 Hz), 2.17−2.10 (1H, m), 2.01−1.93 (2H, m), 1.82−1.76 (1H, m), 1.72 (3H, s), 1.65−1.55 (3H, m), 1.24−1.19 (1H, m); NMR δ_C (125 MHz, $CDCl_3$, 298 K) 148.2 (C), 109.2 (CH_2), 99.6 (C), 74.9 (C), 40.8 (CH), 40.3 (CH_2), 32.0 (CH_2), 27.7 (CH_2), 26.3 (CH_2), 21.3 (CH_3); MS *m*/*z* (ES^+) 357.2037 (M + Na $C_{20}H_{30}NaO_4$ requires 357.2036).

Data for 9: mp 108−110 °C; $[\alpha]^{23}_D$ −30.8 (*c* 0.30 $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3577, 3494, 2943, 2858, 1707, 1644, 1454, 1376, 1129, 1102, 983, 901; NMR δ_H (400 MHz; $CDCl_3$) 4.78 (1H, s), 4.75 (1H, s), 4.72 (1H, s), 4.71 (1H, s), 2.57−2.49 (1H, m), 2.35−2.21 (3H, m), 2.03 (1H, dd, J = 13.8, 5.0 Hz), 1.98−1.91 (1H, m), 1.88−1.80 (4H, m), 1.78−1.68 (7H, m), 1.63−1.48 (7H, m); NMR δ_C (100 MHz, $CDCl_3$, 298 K) 149.2 (C), 148.4 (C), 109.4 (CH_2), 109.1 (CH_2), 107.4 (C), 103.5 (C), 81.3 (C), 69.6 (C), 42.1 (CH), 41.0 (CH_2), 36.3 (CH), 35.9 (CH_2), 34.3 (CH_2), 32.3 (CH_2), 28.3 (CH_2), 28.20 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 21.7 (CH_3), 20.7 (CH_3); MS *m*/*z* (ES^+) 357.2035 (M + Na $C_{20}H_{30}NaO_4$ requires 357.2036).

Synthesis of 16. Spirochroman **2** (60 mg, 0.20 mmol) was dissolved in CH_2Cl_2 (1.50 mL) and cooled to 0 °C, and then *m*-CPBA (44 mg of 70 wt %, 0.18 mmol) was added in one portion. The resulting solution was stirred at 0 °C for 45 min. The reaction was quenched with saturated $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product as a white solid. The crude product was dissolved in CD_3OD (1 mL) and the resulting solution was stirred for 12 h at rt. The solvent was removed in vacuo to give the crude product. Purification by column chromatography (pentane/Et_2O; 20/1) afforded the product **16** (30 mg, 41%) as white crystalline solid: mp 192−195 °C; $[\alpha]^{24}_D$ +58.5 (*c* 1.30 $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3532, 3086, 2991, 2939, 2860, 2216, 2129, 2070, 1710, 1643, 1454, 1361, 1300, 1168, 1115, 1091, 1069, 987; NMR δ_H (400 MHz, $CDCl_3$, 298 K) 4.70 (2H, s), 2.06−2.00 (1H, m), 1.97−1.87 (1H, m), 1.85−1.76 (1H, m), 1.73 (3H, s), 1.71−1.67 (1H, m), 1.66−1.58 (1H, m), 1.56−1.48 (3H, m), 1.43 (1H, dd, J = 13.5, 12.8 Hz); δ_D (61.4 MHz; $CDCl_3$) 3.24 (OCD_3); NMR δ_C (100 MHz, $CDCl_3$, 298 K) 149.5 (C), 108.5 (CH_2), 100.4 (C), 71.9 (C), 40.6 (CH), 34.0 (CH_2), 32.8 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 21.2 (CH_3); MS *m*/*z* (ES^+) 391.2734 (M + Na $C_{22}H_{28}D_6NaO_4$ requires 391.2726).

(+)-Cymbodiacetal Dimethyl Acetal (17). Spirochroman (**2**) (50 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (1.00 mL) and cooled to 0 °C, *m*-CPBA (39 mg of 70 wt %, 0.16 mmol) was added in one portion, and the resulting solution was stirred at 0 °C for 45 min. The reaction was quenched with saturated $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product as a white solid. The crude product was dissolved in MeOH (1 mL), and *p*TSA (3 mg, 0.1 mmol) was added. The resulting solution was stirred for 12 h at rt. The reaction was quenched with saturated $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography (pentane/Et_2O; 20/1) afforded the product **17** (25 mg, 43%) as very thick oil: $[\alpha]^{21}_D$ +48.5 (*c* 0.3 $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3695, 2938, 1643, 1602, 1452, 1375, 1158, 1124, 1096, 1062, 1035, 1014, 894; NMR δ_H (400 MHz, $CDCl_3$, 298 K) 4.70 (2H, s), 3.25 (3H, s), 2.07−2.01 (1H, m), 1.92 (1H, app t, J = 11.5 Hz), 1.85−1.76 (1H, m), 1.73 (3H, s), 1.71−1.40 (6H, m); NMR δ_C (100 MHz, $CDCl_3$, 298 K) 149.6 (C), 108.6 (CH_2), 100.4 (C), 71.9 (C), 47.4 (CH_3), 40.6 (CH), 34.0 (CH_2), 32.9 (CH_2), 27.0 (CH_2), 26.3 (CH_2), 21.2 (CH_3); MS *m*/*z* (ES^+) 385.2333 (M + Na $C_{22}H_{34}NaO_4$ requires 385.2349).

(+)-Cymbodiacetal 1 and Hemiacetal 9. Spirochroman (**2**) (68 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (1.30 mL) and cooled to 0 °C, and then *m*-CPBA (54 mg of 70 wt %, 0.23 mmol) was added in one portion and the resulting solution was stirred at 0 °C for 45 min. The reaction was quenched with saturated $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product as a white solid. *p*TSA (4 mg, 0.02 mmol) was then added to the stirred solution of the above crude product in (1.00 mL) THF/H_2O (1:1). The resulting solution was stirred for 1 h. The reaction was quenched with saturated $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (10 mL), extracted with CH_2Cl_2 (10 mL × 3), dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Purification by column chromatography (pentane/Et_2O; 10/1−4/1−2/1) afforded the products **1** (33 mg, 44%) and **9** (5 mg, 7%) as white crystalline solids.

Data for 1: mp 205−208 °C (lit.[1] mp 206−207 °C); $[\alpha]^{24}_D$ +26.5 (*c* 0.20 $CHCl_3$) (lit.[1] $[\alpha]^{24}_D$ +26 ± 5 (*c* 0.12, $CHCl_3$); IR ν_{max}/cm^{-1} ($CHCl_3$) 3699, 3600, 2928, 2855, 2360, 1602, 1454, 1378, 1112, 1069, 1004, 895; NMR δ_H (400 MHz, $CDCl_3$, 298 K) 4.72 (1H, app t, J = 1.4 Hz), 4.71 (1H, d, J = 0.81 Hz), 2.17−2.10 (2H, m), 2.00−1.92 (1H, m), 1.85−1.75 (2H, m), 1.74−1.67 (4H, m), 1.64−1.50 (3H, m); NMR δ_C (100 MHz, $CDCl_3$, 298 K) 149.0 (C), 109.0 (CH_2), 98.1 (C), 71.8 (C), 41.5 (CH_2), 41.1 (CH), 33.0 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 21.2 (CH_3); NMR δ_C (100 MHz, CD_3OD, 298 K) 150.7 (C), 109.1 (CH_2), 98.9 (C), 72.8 (C), 42.4 (CH), 41.9 (CH_2), 34.1 (CH_2), 27.5 (CH_2), 27.3 (CH_2), 21.1 (CH_3); MS *m*/*z* (ES^+) 357.2034 (M + Na $C_{20}H_{30}NaO_4$ requires 357.2036). These data are in agreement with those previously reported in the isolation paper of cymbodiacetal (**1**) except for the peak originally reported at 75.5 ppm in the ^{13}C NMR ($CDCl_3$).[1] We record this peak at 71.8 ppm and attribute the discrepancy to a typographical error in the original work. The ^{13}C NMR data that we obtained for **1** in CD_3OD matched that reported for the previously reported synthetic sample.[2] The data obtained for the bis-acetal **9** were identical to those recorded previously in this work.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.