Synthesis of Furanoid Terpenes via an Efficient Palladium-Catalyzed Cyclization of 4,6-Dienols

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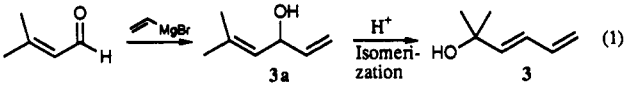
The total syntheses of marmelo oxides A and B and a terpene alcohol found in peppermint oil are described. The key steps in these syntheses are the regioselective palladium-catalyzed allylic substitution of **4** and **11** to **6a** and **12**, respectively, and the regioselective palladium-catalyzed cyclization of **8** and **14** to **9a**, **9b**, and **15**, respectively. The relative stereochemistry of marmelo oxides A and B was established by NOE measurements.

Introduction

Recently, we reported the stereocontrolled palladium-catalyzed cyclization of cyclic 1,3-diene acids to lactones.[1] In connection with that study, we also found that cyclic diene alcohols underwent the corresponding reaction to give tetrahydrofurans.[2] We have now extended the latter reaction to include acyclic diene alcohols and used it to synthesize marmelo oxides A and B (**1a**, **1b**) and terpene alcohol **2** shown in Figure 1. Naturally occurring marmelo oxide exists as a 1:1 mixture of **1a** and **1b** and has been shown[3] to be the characteristic flavor component of the quincefruit (*Cydonia oblonga*). The terpene alcohol **2** occurs in peppermint oil extracted from most species of the *Mentha* family such as *M. piperita*, *M. cardiaca*, and *M. spicata*.[4]

Results and Discussion

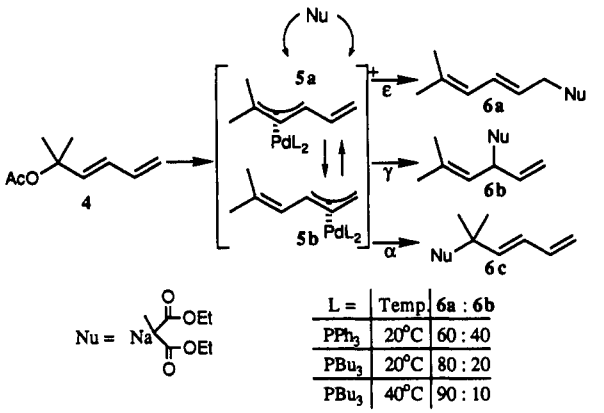
The syntheses of **1a**, **1b**, and **2** utilizing this new palladium-catalyzed cyclization are outlined in Schemes II and III. The synthesis of marmelo oxides A and B (**1a** and **1b**) starts with 2-methyl-3,5-hexadien-2-ol (**3**), readily prepared on a multigram scale from 3,3-dimethylacrolein and vinylmagnesium bromide. The initially product formed, 2-methyl-2,5-hexadien-4-ol (**3a**),[5] is quantitatively converted into **3** during the acidic workup (eq 1).[6]



(1)

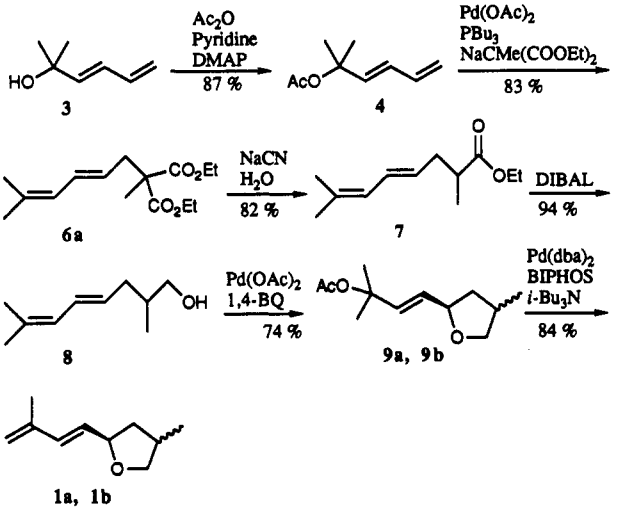
We first tried to isolate[7] **3a** in order to synthesize the diene ester **7** in one step via a Claisen rearrangement with triethyl orthopropionate, but the rearrangement did not occur under the conditions tried.[8] So, instead, **3** was transformed into the allylic acetate **4** (Ac_2O, DMAP, Et_3N) followed by a palladium-catalyzed allylic alkylation. In the latter reaction it was necessary to substitute the acetate in a completely regioselective ϵ-attack. This was accomplished by reaction of **4** with sodium diethyl methylmalonate at 40 °C, which afforded **6** via (π-allyl)palladium intermediates **5a** and **5b** as shown in Scheme I.

Scheme I



L =	Temp	6a : 6b
PPh_3	20°C	60 : 40
PBu_3	20°C	80 : 20
PBu_3	40°C	90 : 10

Scheme II[a]



[a] 1,4-BQ = 1,4-benzoquinone.

In this reaction it was found that the phosphine ligand on palladium had a significant effect on the **6a**:**6b** ratio. The product arising from α-attack (**6c**) was in all cases less than 5%. Initially, PPh_3 was used as ligand, giving a **6a**:**6b** ratio of 60:40, but when PBu_3 was employed as ligand the **6a**:**6b** ratio increased to 80:20. The increased relative yield of **6a** when PPh_3 is replaced with the more electron rich PBu_3 can be explained by a diminished carbonium ion character at the π-allyl carbons in **5**.[9] For further improvement of the relative yield of the desired isomer the

(1) Bäckvall, J. E.; Andersson, P. G.; Vågberg, J. O. *Tetrahedron Lett.* **1989**, *40*, 137.

(2) (a) Unpublished results. (b) For a related spirocyclization, see: Bäckvall, J. E.; Andersson, P. G. *J. Org. Chem.* **1991**, *56*, 2274.

(3) (a) Tsuneya, T.; Ishihara, M.; Shiota, H. *Agric. Biol. Chem.* **1983**, *47*, 2495. (b) Nishida, Y.; Ohrui, H.; Meguro, H. *Agric. Biol. Chem.* **1983**, *47*, 2969.

(4) Sakurai, K.; Takahashi, K.; Yoshida, T. *Agric. Biol. Chem.* **1983**, *47*, 1249.

(5) The synthesis of **3a** is an improvement of an earlier procedure[6] by which **3a** was synthesized in 36% yield.

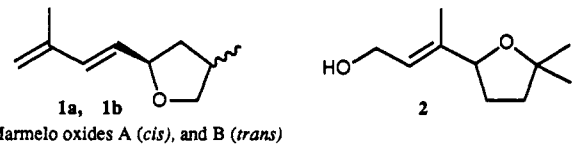
(6) Braude, E. A.; Timmons, C. J. *J. Chem. Soc.* **1950**, 2007.

(7) If acidic workup is omitted, the initially formed product, 2-methyl-2,5-hexadien-4-ol (**3a**), is isolated: ^{1}H NMR δ 5.87 (m, 1 H), 5.26–5.13 (m, 2 H), 5.06 (d, J = 10.5 Hz, 1 H), 4.83 (t, J = 6.8 Hz, 1 H), 1.73 (s, 3 H), 1.70 (s, 3 H).

(8) (a) **3a** (1 equiv), triethyl orthopropionate (10 equiv), and propionic acid (0.1 equiv) were stirred under N_2 for 6 h. (b) It was also attempted to treat the ester formed from **3a** and propionic acid with 1.1 equiv of LDA at rt.

(9) The ligand effect on the regiochemistry of nucleophilic attack by dialkyl malonate anions on (π-allyl)palladium complexes has previously been studied: Åkermark, B.; Zetterberg, K.; Hansson, S., Krakenberger, B. *J. Organomet. Chem.* **1987**, *335*, 133. Åkermark, B.; Krakenberger, B.; Hansson, S. *Organometallics* **1987**, *6*, 620.

0022-3263/91/1956-5349$02.50/0



Marmelo oxides A (*cis*), and B (*trans*)

Figure 1.

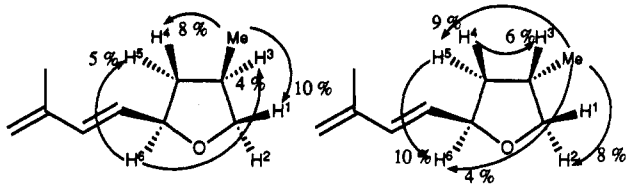


Figure 2.

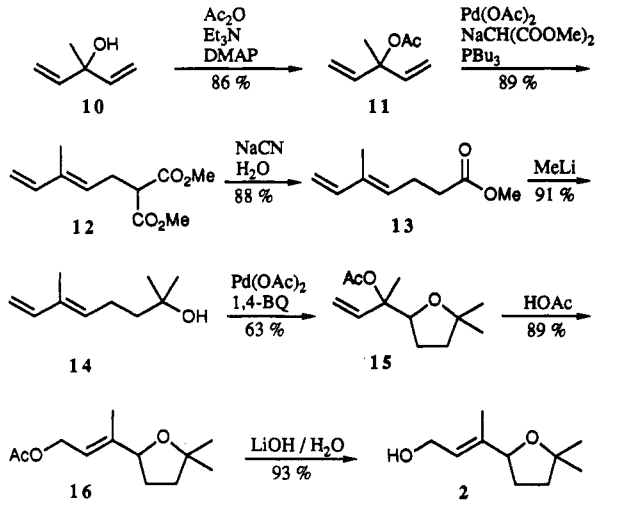
reaction with PBu_3 was run at an elevated temperature (40 °C) and now a **6a**:**6b** ratio of 90:10 was realized. The increased **6a**:**6b** ratio at the elevated temperature is best explained by an isomerization of **6b** to **6a**.[10] The undesired isomer was removed by column chromatography and **6a** (trans:cis = 83:17) was obtained in 83% isolated yield. Compound **6a** was then decarbalkoxylated with NaCN in wet DMSO[11] to give the monoester **7** in a good yield. Reduction of ester **7** with DIBAL at 20 °C in methylene chloride yielded the diene alcohol **8** (Scheme II).

Compound **8** was then subjected to a palladium-catalyzed oxidation ($Pd(OAc)_2$, benzoquinone, HOAc) at 20 °C, which afforded the cyclized product as a 1:1 mixture of diastereomers **9a** and **9b** in 74% isolated yield. These diasteromers were easily separated by column chromatography. In order to suppress formation of the Diels–Alder adduct between the diene and benzoquinone, the diene had to be added slowly to the reaction mixture via syringe pump over 16 h. This reaction, which was performed in acetic acid/acetone,[12] introduced the allylic acetate with the correct regiochemistry (>98% 1,4-addition, >98% *E*). Finally, a highly regioselective (>98%) palladium-catalyzed 1,2-elimination[13] of the allylic acetate in toluene furnished the marmelo oxides A and B as a 1:1 mixture[14] in 84% isolated yield.

In the literature there have appeared conflicting stereochemical assignments[3] of marmelo oxides A and B. Our own assignments of relative stereochemistry, based on the NOE studies summarized in Figure 2, are in agreement with those of Nishida et al.[3b]

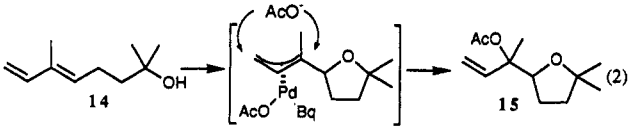
The same basic strategy was employed for the synthesis of the terpene alcohol **2** (Scheme III). The synthesis started with divinylmethylcarbinol (**10**), which is readily available from vinylmagnesium bromide and ethyl acetate.[15] Acetylation of diene alcohol **10** (Ac_2O, DMAP, Et_3N) afforded allylic acetate **11**. Since all attempts[8] to prepare diene ester **13** directly by a Claisen rearrangement of **10** with triethyl orthoacetate failed, the dimethyl malonate derivative **12** was prepared via the same route as for **6**.

Scheme III[a]



[a] 1,4-BQ = 1,4-benzoquinone.

Again, a good regioselectivity (γ:α > 97:3, trans:cis = 80:20) was obtained in the palladium-catalyzed alkylation of the allylic acetate with the malonate ester nucleophile. Subsequent decarbalkoxylation of **12** in DMSO gave **13**, the overall yield of **13** from **11** being 78%. Methyl ester **13** was then transformed in a good yield into the known ocimenol (**14**)[16] by reaction with 2.2 equiv of MeLi. When ocimenol was submitted to the same cyclization conditions as for **8**, allylic acetate **15** was obtained in 63% isolated yield (diastereomeric ratio = 60:40). Surprisingly, an exclusive 1,2-addition had occurred over the 1,3-diene instead of the expected 1,4-addition.[17] The reason for this may be the more pronounced cationic character (vide supra) of the quaternary carbon in the intermediate (π-allyl)-palladium complex (eq 2), which causes the acetate to attack the palladium ligand at the more substituted position.



Bq = 1,4-Benzoquinone

However, it was possible to completely rearrange allylic acetate **15** into the desired, and thermodynamically more stable, isomer **16** by treatment with acetic acid at 100 °C for 24 h. The rearrangement gave a trans:cis mixture in a ratio of 92:8 from which the cis isomer was easily removed by flash chromatography and pure **16** was obtained in 89% isolated yield. The hydrolysis of **16** was performed with LiOH in THF/H_2O at 20 °C, to afford the desired alcohol **2** in high yield.[18]

In conclusion, the syntheses of terpenes **1a**, **1b**, and **2** described above demonstrate the versatility of this palladium-catalyzed cyclization in organic synthesis. It should

(10) A control experiment showed that reaction of **6b** in the presence of $Pd(OAc)_2/PBu_3$ (1:4) in THF at 40 °C for 4 h afforded a 90:10 mixture of **6a**:**6b**: Andersson, P. G. Unpublished results.

(11) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. F.; Jahngren, E. G. E.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

(12) Bäckvall, J. E.; Granberg, K. L.; Hopkins, R. B. *Acta Chem. Scand.* **1990**, *44*, 492.

(13) (a) Trost, B. M.; Fortunak, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 2841. (b) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* **1978**, *19*, 2075. (c) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, *20*, 2301. (d) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.

(14) Attempts to synthesize pure marmelo oxides A and B starting from **9a** and **9b**, respectively, resulted in the same 1:1 isomeric mixture.

(15) Babler, J. H.; Olsen, D. O. *Tetrahedron Lett.* **1974**, *15*, 351.

(16) For an alternative route to ocimenol, see: (a) Ohloff, G.; Seibl, J.; Kovats, E. *Liebig. Ann. Chem.* **1964**, *675*, 83. (b) Kise, H.; Sato, T.; Yasuoka, T.; Seno, M.; Asahara, T. *J. Org. Chem.* **1979**, *44*, 4454.

(17) (a) Bäckvall, J. E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619. (b) Nyström, J. E.; Bäckvall, J. E. *J. Org. Chem.* **1983**, *48*, 3947.

(18) This is an improvement of an earlier procedure[4] in which a mixture of (*E*)- and (*Z*)-**16** was hydrolyzed to give a 2:1 mixture of (*E*)- and (*Z*)-**2** in 83% combined yield.

be noted that in an earlier approach[4] to the terpene alcohol 2, ocimenol (14) was used as an intermediate and was transformed into 2 in four steps with an overall yield of 21% compared with three steps and 52% in the present work. The synthesis of marmelo oxides 1a, 1b reported here is also efficient compared to the earlier procedure[19] in which marmelo oxides A and B were obtained as a mixture in 5.8% overall yield, as compared to 35% in the present work.

Experimental Section

^1H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at 300 and 75.4 MHz, respectively. Mass spectra were recorded in the electron impact mode, using a potential of 70 eV. Toluene and CH_2Cl_2 were distilled from CaH_2 under N_2. THF was distilled from a dark blue benzophenone/sodium ketyl solution under N_2. Commercial acetone (99.5%), acetic acid (99.8%), CCl_4 (99.9%), MeLi (1.6 M in ether), DIBAL (1.0 M in hexanes), and vinylmagnesium bromide (1.0 M in THF) were used as delivered. 1,4-Benzoquinone, 1,2-bis(diphenylphosphino)ethane (dppe), PBu_3, and i-Bu_3N were purchased from Aldrich. $Pd(dba)_2$ was prepared according to ref 20. $Pd(OAc)_2$ was supplied by Engelhard, Gloucestershire, England. Merck silica gel 60 (240–400 mesh) was used for column chromatography.

(*E*)-2-Methyl-3,5-hexadien-2-ol (3). To a solution of vinylmagnesium bromide (200 mL, 1 M in THF, 200 mmol) under N_2 was slowly added 3,3-dimethylacrolein (15 g, 178 mmol) at 0 °C, and the mixture was then stirred for 30 min. Brine (100 mL) and HCl (30 mL, 6 M) were added[7] and the resulting two phases were separated. The organic phase was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography of the residue (pentane/ether 75:25) afforded 3[6] (14.5 g, 129 mmol, 73%): n^{20}_D 1.4761; ^1H NMR δ 6.39–6.18 (m, 2 H), 5.84 (d, J = 14.9 Hz, 1 H), 5.21 (dd, J = 1.9, 16.3 Hz, 1 H), 5.08 (dd, J = 1.9, 10.0 Hz, 1 H), 1.84 (s, 1 H), 1.34 (s, 6 H); ^{13}C NMR δ 141.7, 136.6, 127.2, 117.0, 70.6, 29.6.

(*E*)-2-Methyl-2,5-hexadien-2-yl Acetate (4). To (*E*)-2-methyl-3,5-hexadien-2-ol[6] (3) (12 g, 107 mmol) under N_2 were added acetic anhydride (25 g, 250 mmol), triethylamine (25 g, 250 mmol), and DMAP (1.5 g, 12.5 mmol) at 0 °C. The mixture was then allowed to sir at rt for 18 h. When the reaction was complete, pentane/ether (200 mL, 1:1) was added and the resulting solution was washed with water (4 × 50 mL) and brine (25 mL) and dried ($MgSO_4$). Evaporation of the solvent and chromatography using pentane/ether (90:10) as eluent afforded 4 (14.3 g, 92.7 mmol, 87%) as a clear colorless liquid: ^1H NMR δ 6.38–6.13 (m, 2 H), 5.97 (dd, J = 2.3, 15.5 Hz, 1 H), 5.22 (app dt, J = 2.0, 16.2 Hz, 1 H), 5.10 (app dt, J = 2.0, 9.7 Hz, 1 H), 1.98 (s, 3 H), 1.54 (s, 6 H); ^{13}C NMR δ 170.0, 137.9, 136.5, 128.9, 117.6, 80.2, 26.7, 22.3; IR (CCl_4) 2980, 1739, 1366, 1248, 1117, 1004; MS, m/z 154 (M^+, 10), 112 (12), 97 (19), 95 (21), 79 (25), 43 (100).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.85; H, 8.94.

Diethyl 2-Methyl-2-((*E*)-5-methyl-2,4-hexadien-1-yl)-malonate (6a). To a slurry of NaH (1.46 g, 80% in oil, 48.64 mmol) in dry THF (500 mL) under N_2 were added diethyl methylmalonate (8.47 g, 48.64 mmol), PBu_3 (1.57 g, 7.78 mmol), and $Pd(OAc)_2$ (437 mg, 1.95 mmol). To the resulting yellow solution was then added the acetate 4 (50 g, 32.43 mmol), and the reaction mixture was allowed to stir for 3 h at 40 °C. The reaction mixture was then washed with water (2 × 150 mL) and brine (75 mL) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography (pentane/ether 75:25) afforded **6a** (7.20 g, *E*:*Z* = 83:17, 26.8 mmol, 83%) as a clear colorless oil: ^1H NMR δ 6.27 (dd, J = 10.8, 14.9 Hz, 1 H), 5.77 (d, J = 10.8, 1 H), 5.40 (app dt, J = 7.5, 14.9 Hz, 1 H), 4.18 (app tq, J = 1.6, 7.1 Hz, 4 H), 2.64 (d, J = 7.5 Hz, 2 H), 1.74 (s, 3 H), 1.72 (s, 3 H), 1.38 (s, 3 H), 1.24 (t, J = 7.1 Hz, 6 H); ^{13}C NMR δ 172.0, 134.4, 130.9, 128.2, 124.5, 61.1, 53.8, 39.1, 25.9, 19.7, 18.2, 14.0; IR (CCl_4) 2982, 2937, 2911, 1733, 1240, 1106; MS, m/z 268 (M^+, 13), 194 (47), 121 (43), 95 (100), 29 (57).

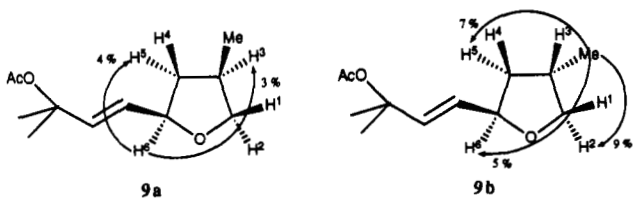


Figure 3.

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02. Found: C, 66.89; H, 9.01.

Ethyl (*E*)-2,7-Dimethyl-4,6-octadienoate (7). A solution of **6a** (3.50 g, 13.04 mmol), NaCN (3.20 g, 65.22 mmol), and H_2O (1.17 g, 65.22 mmol) in DMSO (100 mL) under N_2 was stirred for 5 h at 170 °C. When the reaction was complete, H_2O (100 mL) was added and the resulting mixture was extracted with pentane (3 × 50 mL). The combined pentane fractions were washed with H_2O (30 mL) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography (pentane/ether 90:10) afforded 7 (2.10 g, 10.70 mmol, *E*:*Z* = 83:17, 82%) as a clear colorless oil: ^1H NMR δ 6.25 (dd, J = 10.8, 14.9 Hz, 1 H), 5.77 (d, J = 10.8 Hz, 1 H), 5.47 (app dt, J = 7.3, 14.9 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 2.54–2.38 (m, 2 H), 2.28–2.15 (m, 1 H), 1.75 (s, 3 H), 1.73 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.15 (d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 176.2, 133.8, 128.9, 127.8, 124.7, 60.2, 39.8, 36.9, 25.9, 18.2, 16.6, 14.2; IR (CCl_4) 2978, 2934, 2912, 1734, 1162; MS, m/z 196 (M^+, 16), 122 (26), 107 (23), 95 (100), 67 (36), 55 (25).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.22; H, 10.42.

(*E*)-2,7-Dimethyl-4,6-octadien-1-ol (8). To a solution of DIBALH (23 mL, 1 M in hexanes, 22.42 mmol) under N_2 was slowly added ester 7 at 0 °C. After 30 min of stirring, H_2O (50 mL) was added and the resulting mixture extracted with ether (3 × 50 mL). The combined ethereal fractions were washed with brine (25 mL) and dried ($MgSO_4$). Concentration under reduced pressure and subsequent chromatography (pentane/ether 75:25) gave 8 (1.48 g, 9.58 mmol, *E*:*Z* = 90:10, 94%) as a clear colorless oil: ^1H NMR δ 6.25 (dd, J = 10.8, 14.9 Hz, 1 H), 5.80 (d, J = 10.8 Hz, 1 H), 5.54 (app dt, J = 7.4, 14.9 Hz, 1 H), 3.54–3.42 (m, 2 H), 2.20 (ddd, J = 7, 7, 14 Hz, 1 H), 1.98 (ddd, J = 7, 7, 14 Hz, 1 H), 1.78–1.66 (m, 1 H), 1.76 (s, 3 H), 1.74 (s, 3 H), 1.53 (s, 1 H), 0.92 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 133.3, 129.4, 128.3, 124.8, 67.9, 36.8, 36.2, 25.9, 18.2, 16.4; IR (CCl_4) 3640, 2965, 2913, 2874, 1439, 1377, 1037; MS, m/z 154 (M^+, 32), 121 (21), 95 (100), 67 (88), 55 (59), 41 (75).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 78.07; H, 11.45.

2-((*E*)-3-Acetoxy-3-methyl-1-buten-1-yl)-4-methyltetrahydrofuran (9). To a solution of $Pd(OAc)_2$ (58.1 mg, 0.259 mmol) and benzoquinone (1.12 g, 10.4 mmol) in acetone/HOAc (20 mL, 4:1) was added 8 (0.80 g, 5.19 mmol) by syringe pump during 16 h. After a further 36 h, ether (75 mL) was added to the reaction mixture and the resulting solution was washed with NaOH (2 × 20 mL, 2 M), H_2O (15 mL), and brine (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure and subsequent chromatography of the residue (pentane/ether 90:10) yielded 9 (0.81 g, 3.82 mmol, >98% *E*, 74%) as a 1:1 mixture of cis and trans diastereomers. These were separated by column chromatography to afford pure samples, the stereochemistry being assigned by NOE measurements shown in Figure 3.

9a (trans): ^1H NMR δ 5.92 (dd, J = 1.1, 15.6 Hz, 1 H), 5.61 (dd, J = 6.5, 15.6 Hz, 1 H), 4.42 (app q, J = 6.5 Hz, 1 H), 4.03 (dd, J = 6.9, 8.1 Hz, 1 H), 3.31 (dd, J = 7.0, 8.1 Hz, 1 H), 2.36 (app sext, J = 6.9 Hz, 1 H), 1.97 (s, 3 H), 1.87–1.77 (m, 1 H), 1.74–1.63 (m, 1 H), 1.52 (s, 3 H), 1.51 (s, 3 H), 1.04 (d, J = 6.7 Hz, 3 H); ^{13}C NMR δ 170.0, 135.2, 129.5, 80.1, 78.6, 75.1, 40.2, 33.1, 26.9, 26.4, 22.3, 17.7; IR ($CDCl_3$) 2964, 2933, 2873, 1727, 1369, 1260; MS, m/z 212 (M^+, 0.1), 152 (20), 85 (100), 69 (36), 43 (90).

9b (cis): ^1H NMR δ 5.95 (dd, J = 1.0, 15.7 Hz, 1 H), 5.65 (dd, J = 6.9, 15.7 Hz, 1 H), 4.31 (m, 1 H), 3.93 (app t, J = 7.8 Hz, 1 H), 3.39 (app t, J = 8.0 Hz, 1 H), 2.44–2.29 (m, 1 H), 2.27–2.16 (m, 1 H), 1.98 (s, 3 H), 1.53 (s, 3 H), 1.51 (s, 3 H), 1.33–1.20 (m, 1 H), 1.05 (d, J = 6.5 Hz, 3 H); ^{13}C NMR δ 170.0, 135.6, 129.5, 80.1, 78.6, 74.7, 41.4, 34.6, 26.9, 26.3, 22.3, 17.5; IR ($CDCl_3$) 2965, 2932, 2873, 1727, 1369, 1259; MS, m/z 212 (M^+, 0.1), 152 (19),

(19) Srikrishna, A.; Krishnan, K. *J. Org. Chem.* **1989**, *54*, 3981.
(20) Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1977**, *17*, 135.

98 (14), 85 (100), 69 (33), 43 (85).

Anal. Calcd for $C_{12}H_{20}O_3$ (isomer mixture): C, 67.89; H, 9.50. Found: C, 67.72; H, 9.33.

Marmelo Oxides A and B (1a, 1b). To a solution of dppe (19.1 mg, 0.0471 mmol) and triisobutylamine (131 mg, 0.707 mmol) in toluene (1 mL) under N_2 were added $Pd(dba)_2$ (13.6 mg, 0.0236 mmol) and **9** (100 mg, 0.471 mmol). The reaction mixture was heated at reflux for 2 h, cooled to rt, diluted with ether (5 mL), and washed with aqueous HCl (2 × 2 mL, 2 M). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was chromatographed (pentane) to give marmelo oxides A and B as a 1:1 mixture (60 mg, 0.394 mmol, >98% *E*, 84%). The spectral data are in agreement with those reported in the literature.[3b]

Marmelo oxide A (cis): ^1H NMR δ 6.31 (d, *J* = 15.6 Hz, 1 H), 5.67 (dd, *J* = 7.1, 15.7 Hz, 1 H), 4.96 (br s, 2 H), 4.38 (app ddt, *J* = 0.8, 6.6, 9.4 Hz, 1 H), 3.94 (app t, *J* = 7.8 Hz, 1 H), 3.41 (app t, *J* = 8.1 Hz, 1 H), 2.43–2.31 (m, 1 H), 2.26–2.17 (m, 1 H), 1.85 (app t, *J* = 1.0 Hz, 3 H), 1.29 (app dt, *J* = 9.5, 12.0 Hz, 1 H), 1.06 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR δ 140.9, 132.7, 130.1, 116.0, 78.5, 74.3, 40.0, 32.8, 18.0, 17.0.

Marmelo oxide B (trans): ^1H NMR δ 6.30 (d, *J* = 15.6 Hz, 1 H), 5.64 (dd, *J* = 7.0, 15.6 Hz, 1 H), 4.96 (br s, 2 H), 4.49 (app q, *J* = 6.8 Hz, 1 H), 4.05 (dd, *J* = 6.9, 7.3 Hz, 1 H), 3.33 (dd, *J* = 6.9, 8.2 Hz, 1 H), 2.44–2.31 (m, 1 H), 1.89–1.79 (m, 1 H), 1.84 (app t, *J* = 1.0 Hz, 3 H), 1.75–1.66 (m, 1 H), 1.05 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR δ 140.9, 133.1, 130.2, 116.1, 80.1, 74.6, 41.2, 34.2, 18.0, 17.3.

3-Methyl-1,4-pentadien-3-yl Acetate (11). To 3-methyl-1,4-pentadien-3-ol[11] (0.69 g, 7.05 mmol) under N_2 were added acetic anhydride (1.43 g, 14.09 mmol), triethylamine (1.43 g, 14.09 mmol), and DMAP (86 mg, 0.705 mmol) at 0 °C. The mixture was allowed to stir at rt for 24 h. When reaction was complete, pentane/ether (20 mL, 1:1) was added, and the resulting solution was washed with water (4 × 5 mL) and brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography (pentane/ether 90:10) afforded **11** (0.85 g, 6.06 mmol, 86%) as a clear colorless liquid: ^1H NMR δ 6.06 (dd, *J* = 10.8, 17.4 Hz, 2 H), 5.23 (dd, *J* = 0.8, 17.4 Hz, 2 H), 5.17 (dd, *J* = 0.8, 10.8 Hz, 2 H), 2.03 (s, 3 H), 1.61 (s, 3 H); ^{13}C NMR δ 169.7, 140.4, 114.1, 81.9, 24.0, 22.1; IR (CCl_4) 2985, 2937, 1741, 1367, 1244; MS, *m/z* 140 (M^+, 0.7), 80 (23), 79 (21), 43 (100).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.48; H, 8.49.

Dimethyl (*E*)-(3-Methyl-2,4-pentadien-1-yl)malonate (12). To a slurry of NaH (270 mg, 80% in oil, 8.93 mmol) in dry THF (100 mL) under N_2 were added dimethyl malonate (1.20 g, 8.93 mmol), PBu_3 (290 mg, 1.43 mmol), and $Pd(OAc)_2$ (80 mg, 0.36 mmol). To the resulting yellow solution was then added acetate **11** (0.83 g, 5.94 mmol), and the reaction mixture was allowed to stir for 3 h at 40 °C. The reaction mixture was then washed with water (2 × 30 mL) and brine (15 mL) and dried ($MgSO_4$). Concentration under reduced pressure and chromatography (pentane/ether 75:25) afforded **12** (1.12 g, *E*:*Z* = 80:20, 5.29 mmol, 89%) as a clear colorless oil: ^1H NMR δ 6.33 (dd, *J* = 10.8, 17.4 Hz, 1 H), 5.40, (app t, *J* = 7.5 Hz, 1 H), 5.14 (d, *J* = 17.4 Hz, 1 H), 4.99 (d, *J* = 10.8 Hz, 1 H), 3.74 (s, 6 H), 3.43 (app t, *J* = 7.6 Hz, 1 H), 2.75 (app t, *J* = 7.4 Hz, 2 H), 1.77 (s, 3 H); ^{13}C NMR δ 169.3, 140.8, 136.7, 127.1, 112.0, 52.6, 51.5, 27.7, 11.7; IR (CCl_4) 2953, 1759, 1740, 1436, 1224, 1153; MS, *m/z* 212 (M^+, 11), 152 (23), 93 (100), 81 (53).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.15; H, 7.46.

Methyl (*E*)-5-Methyl-4,6-heptadienoate (13). A solution of **12** (1.10 g, 5.18 mmol), NaCN (1.27 g, 25.9 mmol), and H_2O (0.47 g, 25.9 mmol) in DMSO (75 mL) was stirred for 36 h at 80 °C. When the reaction was complete H_2O (75 mL) was added, and the resulting mixture was extracted with pentane (3 × 50 mL). The combined pentane fractions were washed with H_2O (30 mL) and dried ($MgSO_4$). Concentration under reduced pressure and subsequent chromatography (pentane/ether 90:10) afforded **13** (0.70 g, 4.54 mmol, *E*:*Z* = 80:20, 88%) as a clear colorless oil: ^1H NMR δ 6.35 (dd, *J* = 10.7, 17.2 Hz, 1 H), 5.45 (app t, *J* = 6.9 Hz, 1 H), 5.12 (d, *J* = 17.2 Hz, 1 H), 4.96 (d, *J* = 10.7 Hz, 1 H), 3.68 (s, 3 H), 2.55–2.34 (m, 4 H), 1.76 (s, 3 H); ^{13}C NMR δ 173.4, 141.1, 135.2, 130.4, 111.3, 51.6, 33.8, 23.7, 11.6; IR (CCl_4) 2951, 1743, 1436, 1159; MS, *m/z* 154 (M^+, 56), 95 (61), 94 (49), 81 (63), 79 (100).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.97; H, 8.99.

(*E*)-2,6-Dimethyl-5,7-octadien-2-ol (14). To a solution of MeLi (6.5 mL, 1.6 M in ether, 10.12 mmol) under N_2 was slowly added a solution of **13** (0.65 g, 4.21 mmol) in ether (5 mL) at 0 °C. After 30 min of stirring, H_2O (20 mL) and HCl (5 mL, 2 M) were added, and the resulting mixture was extracted with ether (3 × 10 mL). The combined ethereal fractions were washed with brine (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure and subsequent chromatography of the residue using pentane/ether (75:25) as eluent afforded **14** (0.59 g, 3.83 mmol, *E*:*Z* = 87:13, 91%) as a clear colorless oil. The spectral data are in accordance with those reported.[16] **14:** ^1H NMR δ 6.36 (dd, *J* = 10.7, 17.4 Hz, 1 H), 5.50 (app t, *J* = 7.3 Hz, 1 H), 5.09 (d, *J* = 10.7 Hz, 1 H), 4.93 (d, *J* = 17.4 Hz, 1 H), 2.28–2.18 (m, 2 H), 1.76 (s, 3 H), 1.59–1.52 (m, 2 H), 1.43 (s, 1 H), 1.24 (s, 6 H); ^{13}C NMR δ 141.4, 134.1, 132.8, 110.6, 70.9, 43.1, 29.2, 23.2, 11.6; IR (neat) 3400, 2971, 1642, 1606, 1378, 1127, 989, 892; MS, *m/z* 154 (M^+, 1.3), 136 (39), 121 (33), 93 (100), 81 (67), 79 (40), 59 (82).

2-(2-Acetoxy-3-buten-2-yl)-5,5-dimethyltetrahydrofuran (15). To a solution of $Pd(OAc)_2$ (36.4 mg, 0.162 mmol) and benzoquinone (0.70 g, 6.48 mmol) in acetone/HOAc (20 mL, 4:1) was added **14** (0.50 g, 3.24 mmol) by syringe pump during 24 h. After another 48 h, ether (75 mL) was added to the reaction mixture and the resulting solution was washed with NaOH (2 × 20 mL, 2 M), H_2O (15 mL), and brine (10 mL) and dried ($MgSO_4$). Concentration under reduced pressure and subsequent chromatography of the residue (pentane/ether 75:25) yielded **15** (0.43 g, 2.03 mmol, 63%) as a 60:40 mixture of two diastereomers: ^1H NMR (major isomer) δ 5.99 (dd, *J* = 11.0, 17.6 Hz, 1 H), 5.24–5.14 (m, 2 H), 4.05 (app t, *J* = 7.2 Hz, 1 H), 2.03 (s, 3 H), 1.95–1.84 (m, 2 H), 1.70 (app t, *J* = 7.4 Hz, 2 H), 1.55 (s, 3 H), 1.22 (br s, 6 H); ^{13}C NMR (major isomer) δ 170.0, 139.2, 114.9, 83.9, 83.6, 81.6, 38.2, 28.4, 28.0, 26.8, 22.3, 19.1; IR (CCl_4) 2973, 1741, 1367, 1250, 1067; MS, *m/z* 212 (M^+, 0.03), 152 (11), 99 (77), 81 (84), 71 (25), 55 (27), 43 (100); ^1H NMR (minor isomer) δ 5.99 (dd, *J* = 11.0, 17.6 Hz, 1 H), 5.22–5.15 (m, 2 H), 4.13 (app t, *J* = 7.2 Hz, 1 H), 2.03 (s, 3 H), 1.95–1.65 (m, 4 H), 1.55 (s, 3 H), 1.22 (br s, 6 H).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.65; H, 9.31.

2-((*E*)-4-Acetoxy-2-buten-2-yl)-5,5-dimethyltetrahydrofuran (16). A solution of **15** (0.40 g, 1.89 mmol) in HOAc (5 mL) under N_2 was stirred for 24 h at 100 °C, cooled to rt, diluted with H_2O (10 mL), and extracted with pentane (4 × 5 mL). The combined pentane fractions were washed with H_2O (5 mL) and dried with $MgSO_4$. Concentration under reduced pressure gave a 92:8 mixture of *E* and *Z* isomers of **16**, which was purified by flash chromatography (pentane/ether 90:10) to give pure *E* isomer **16** (0.36 g, 1.68 mmol, >98% *E*, 89%) as a clear, colorless oil. The spectral data are in agreement with those reported in the literature.[4] **16:** ^1H NMR δ 5.66 (app dt, *J* = 1.2, 7.0 Hz, 1 H), 4.63 (d, *J* = 7.0 Hz, 2 H), 4.34 (app t, *J* = 7.0 Hz, 1 H), 2.07 (m, 1 H), 2.05 (s, 3 H), 1.73–1.64 (m, 3 H), 1.68 (s, 3 H), 1.29 (s, 3 H), 1.26 (s, 3 H); ^{13}C NMR δ 171.1, 141.7, 118.6, 82.6, 81.1, 61.0, 38.6, 31.2, 28.7, 28.1, 21.0, 12.4.

(*E*)-3-(5′,5′-Dimethyltetrahydrofuran-2′-yl)-2-buten-1-ol (2). A solution of LiOH (0.12 g, 4.95 mmol) and **16** (0.35 g, 1.65 mmol) in THF/H_2O (10 mL, 1:1) was stirred for 12 h at 20 °C. Water (20 mL) was then added and the resulting solution was extracted with ether (4 × 5 mL). The combined ethereal fractions were washed with brine (5 mL) and dried ($MgSO_4$). Concentration under reduced pressure and subsequent chromatography (pentane/ether 50:50) yielded **2** (0.26 g, 1.53 mmol, >98% *E*, 93%) as a clear, colorless oil. The spectral data are in agreement with those reported in the literature.[4] **2:** ^1H NMR δ 5.64 (app t, *J* = 6.6 Hz, 1 H), 4.28 (app t, *J* = 6.7 Hz, 1 H), 4.11 (d, *J* = 6.6 Hz, 2 H), 2.4 (br s, 1 H), 1.99 (m, 1 H), 1.80–1.67 (m, 3 H), 1.59 (s, 3 H), 1.23 (s, 3 H), 1.21 (s, 3 H); ^{13}C NMR δ 138.4, 124.4, 82.9, 81.0, 58.8, 38.5, 30.9, 28.6, 28.0, 11.9.

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Registry No. (±)-**1a**, 121009-51-6; (±)-**1b**, 121009-48-1; (±)-**2**, 134486-02-5; **3**, 69514-47-2; **4**, 134486-03-6; (*E*)-**6a**, 134486-04-7; (*Z*)-**6a**, 134486-17-2; **6b**, 134486-11-6; **6c**, 134486-13-8; (±)-(*E*)-**7**, 134486-05-8; (±)-(*Z*)-**7**, 134486-18-3; (±)-(*E*)-**8**, 134486-06-9; (±)-(*Z*)-**8**, 134566-46-4; (±)-**9a**, 134486-07-0; (±)-**9b**, 134486-12-7; **10**, 918-86-5; **11**, 124177-30-6; (*E*)-**12**, 134486-08-1; (*Z*)-**12**, 134486-14-9; (*E*)-**13**, 134486-09-2; (*Z*)-**13**, 134486-15-0; (*E*)-**14**, 7643-60-9; (*Z*)-**14**, 7643-59-6; (±)-**15** (isomer 1), 134486-10-5; (±)-**15** (isomer 2), 134486-16-1; (±)-(*E*)-**16**, 134528-79-3; (±)-(*Z*)-**16**, 134486-19-4; $(CH_3)_2C{=}CHCHO$, 107-86-8.

Diels-Alder Reactions of a Bicyclic, Cross-Conjugated Dienone[1]

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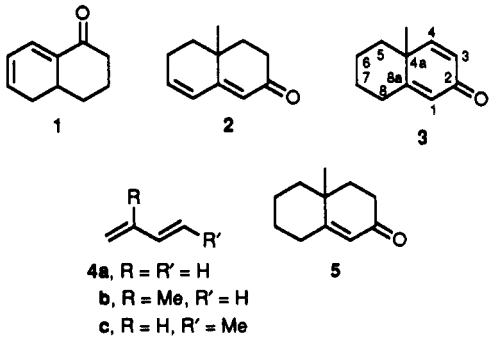
Aluminum chloride catalyzed Diels-Alder reactions of a bicyclic dienone of the 2,5-cyclohexadienone type with 1,3-butadiene, isoprene, and (*E*)-piperylene are described. Structure analysis of the adducts by NMR spectroscopy is presented. The site selectivity and face diastereoselectivity of the reactions are discussed.

Whereas acyclic and cyclic conjugated dienones constitute a class of dienophiles[2] interesting from the points of view of both theory and synthesis, little attention has been devoted to these substances thus far. To overcome in part this information void, the Diels-Alder reactions of simple, acyclic dienes with dienones of the hexalin type, bicycles **1**[3] and **2**,[4] have been investigated recently and



followed by the present study of the cycloaddition behavior of the cross-conjugated hydronaphthalenone **3**. As in the earlier studies, the principal goal of the present investigation was the discovery of the site selectivity, regioselectivity, and diastereoselectivity of the Diels-Alder reaction. In this connection, reactions with 1,3-butadiene (**4a**), isoprene (**4b**), and (*E*)-piperylene (**4c**) were undertaken.

The cycloadditions of hexalone **3**, prepared by oxidation of octalone **5**[5] with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ),[6] were carried out at 55 °C in toluene solution under aluminum chloride catalysis, the dienes and dienophile being employed in a variety of combinations. Interaction of hexalone **3** with 1,3-butadiene (**4a**) led to tricyclic ketones **8a**, **9a**, **6a**, and **7a** in 3.8:2.2:1.2:1 ratio and 68% yield and to tetracyclic ketone **10** in 8% yield. Exposure of dienone **3** to isoprene (**4b**) afforded tricyclic ketones **8b**, **9b**, **6b**, and **7b** in 10.4:2.9:2.3:1 ratio and 40% yield. Finally, mixing of ketone **3** with (*E*)-piperylene (**4c**) furnished an 8.6:2.4:1.8:1 mixture of tricyclic ketones **8c**, **6c**, **9c**, and **7c** in 68% yield. The Diels-Alder adducts **6** and **8** had been isomerized partly into tricycles **7** and **9**, respectively, in the acidic environment of the reaction conditions. The true equilibria, established by treatment of each isomer with ethanolic sodium ethoxide,[7] corresponded to 1.2, 1.2, and 0.036 for the **6a**/**7a**, **6b**/**7b**, and **6c**/**7c** epimer pairs, respectively, and 4.6, 3.5, and 0.25 for the **8a**/**9a**, **8b**/**9b**, and **8c**/**9c** bridgehead isomer couples, respectively. The Diels-Alder products were kinetically based, as shown by the constancy of the (**8** + **9**)/(**6** + **7**) product ratios through the course of each reaction and the absence of any cross-over reaction from **8** or **9** to **6** or **7** occurring on exposure of any adduct to the reaction conditions of the cycloaddition process.

Product Structures. The tricyclic Diels-Alder adducts can be divided into two classes of structurally distinct α,β-unsaturated ketones, those containing a trisubstituted, conjugated double bond (i.e., ketones **8** and **9**) and those with a disubstituted equivalent function (i.e., ketones **6** and **7**). These two groups of cycloaddition products were recognized readily by NMR spectroscopy. Furthermore, the base-induced equilibrations revealed each group being made up of two epimer pairs (**6**-**7** and **8**-**9**). The structures

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