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# Organocatalytic Asymmetric Robinson Annulation of α,β-Unsaturated Aldehydes: Applications to the Total Synthesis of (+)-Palitantin

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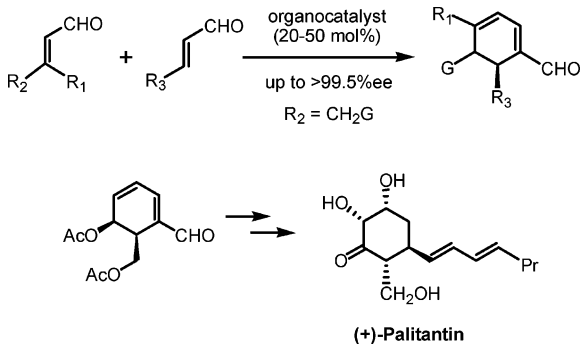


**(+)-Palitantin**

The highly enantioselective organocatalytic Robinson annulation of α,β-unsaturated aldehydes was achieved, catalyzed by L-proline and trialkylamines and providing the formal [4 + 2] cycloaddition adducts. Additionally, in some examples in the catalysis with diarylpyrrolinol silyl ethers, the reactions afforded the [4 + 2] adducts with high enantioselectivity (>99.5% ee). The structure of the adduct, obtained from the reaction of 3-methylbut-2-enal and (*E*)-3-(2-nitrophenyl)acrylaldehyde, was confirmed by X-ray analysis. The absolute configurations of some [4 + 2] cycloadducts were investigated, and the methodology was applied in the synthesis of (+)-palitantin.

## Introduction

The development of [4 + 2] cycloaddition, such as the Diels−Alder reaction, for asymmetric synthesis remains an important challenge in organic synthesis.[1] Recently, organocatalysis in asymmetric synthesis has received extensive attention and has become a burgeoning subject due to its many merits, which include its environmental benignness, high enantioselectivity, low cost, ease of handling, and low toxicity.[2] MacMillan's imidazolidinone catalyst was first demonstrated in the highly enantioselective Diels−Alder reaction of α,β-unsaturated aldehydes with dienes, such as cyclopentadiene, cyclohexadiene, and 1,3-butadienes.[3] The intramolecular Diels−Alder variant with this catalyst has led to the successful total synthesis of solanapyrone D[4] and (+)-hapalindole Q.[5] An examination of imidazolidinone catalysis by density functional theory was performed by Houk and Gordillo.[6] Other organocatalysts for

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asymmetric Diels−Alder reactions include chiral amidinium for the synthesis of the skeleton of estrone and norgestrel,[7] protonated 1,2-diamino-1,2-diphenylethane,[8] chiral triamines for the reaction with α-acyloxyacroleins,[9] chiral ammonium salt of 1,2-diamine for the direct self-Diels−Alder reactions of α,β-unsaturated ketones,[10] hydrazide for the reaction in aqueous media,[11] as well as the hetero-Diels−Alder reaction by TADDOL,[12] inverse-electron-demand hetero-Diels−Alder reaction of nitroso alkenes by pyrrolidine,[13] domino Knoevenagel/hetero-Diels−Alder/elimination reactions by proline,[14] and organocatalytic Diels−Alder reactions on solid supports.[15]

While many organocatalytic [4 + 2] reactions have been reported as described above, the organocatalytic [4 + 2] reaction of α,β-unsaturated aldehydes with high enantioselectivity remains elusive, even with considerable efforts.[16] We report here the highly enantioselective organocatalytic [4 + 2] reaction of α,β-unsaturated aldehydes[17] and its application to the synthesis of (+)-palitantin.

## Results and Discussion

**1. Reactions and Optimizations in the Formal [4 + 2] Cycloaddition of α,β-Unsaturated Aldehydes.** At the outset of our investigation, a series of organocatalysts was screened for the [4 + 2] reactions of 3-methylbut-2-enal and crotonaldehyde (Table 1).[18,19] Among them, L-proline (**I**) and the catalysts **IV**, **X**, and **XII** were promising candidates for the transformation at ambient temperature. Notwithstanding the fact that MacMillan's second-generation imidazolidinone catalyst (**X**) has provided high enantioselectivity in the reaction of cyclopentadiene with α,β-unsaturated aldehydes,[3] moderate enantioselectivity was observed in this reaction (see entries 13 and 14, Table 1). The reactions catalyzed by these promising catalysts at lower temperature (e.g., 0 °C) resulted in slow conversion and decreased enantioselectivity. However, in the cases of **I**, **XIV**, and **XV**, higher enantioselectivity was achieved at lower temperature (entries 2, 20, and 22, Table 1). Unfortunately, when reacted below 0 °C, these reactions either proceed very slowly (after a few days) or not at all. This is an obstacle to increasing enantioselectivity by lowering the reaction temperature. Recently, cocatalysts have been reported to affect the reaction's chemoselectivity and stereoselectivity.[20] As such, tertiary amines were used as the organocatalysts in cyclopropanation,[21] the Baylis−Hillman reaction,[22] and asymmetric conjugate additions by cinchona alkaloids.[23]

Accordingly, in the attempts to improve the reaction rate and ee value, we observed the acceleration of transformation in the presence of trialkylamines.[24] Encouraged by this observation, we surveyed a range of trialkylamine cocatalysts as well as other reaction conditions in an effort to facilitate the reaction and improve enantioselectivity. The results are summarized in Table 2.[25] Reaction of L-proline at −20 °C gave adduct **3a** in higher

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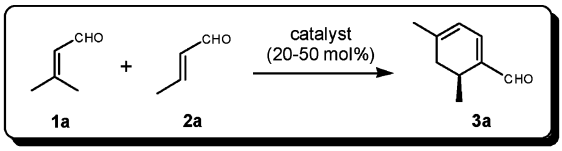
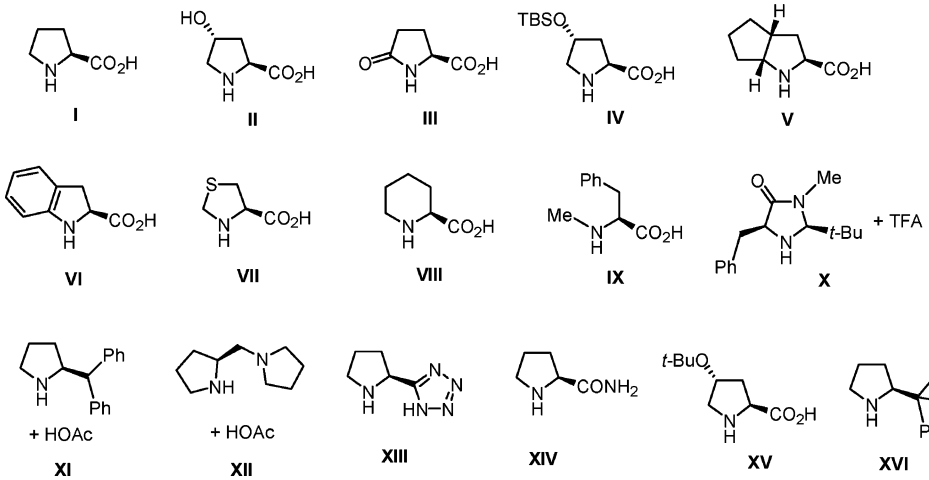
(25) Individual exposure to L-Pro of **1a** or **2a** gave the corresponding self-[4 + 2]- and self-[3 + 3]-cycloaddition adducts, respectively. However, in the reaction of the mixture of **1a**, **2a**, and L-Pro, cross-[4 + 2]-cycloaddition was dominant and less than 5% yields of the self-condensation adducts were observed.

**TABLE 1. Catalyst Screening for the Direct Catalytic Asymmetric [4 + 2] Reaction of 3-Methylbut-2-enal (1a) and Crotonaldehyde (2a) in $CH_3CN$**



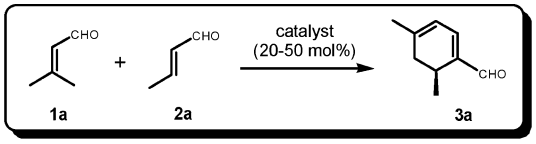

| entry | catalyst | *T* (°C) | time (h) | yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **I** | 25 | 1.5 | 82 | **22** |
| 2 | **I** | −5 | 24 | 84 | 32 |
| 3 | **II** | 25 | 40 | NR | NA |
| 4 | **II** | reflux | 8 | 80 | 7 |
| 5 | **III** | 25 | 24 | NR | NA |
| 6 | **IV** | 25 | 1 | 74 | **24** |
| 7 | **IV** | 0 | 3 | 70 | 21 |
| 8 | **V** | 25 | 192 | 60 | 4 |
| 9 | **VI** | 32 | 4 | ∼0[c] | NA |
| 10 | **VII** | 25 | 32 | NR | NA |
| 11 | **VIII** | 25 | 16 | NR | NA |
| 12 | **IX** | 25 | 24 | NR | NA |
| 13 | **X** | 34 | 3 | 52 | **24** |
| 14 | **X** | 0 | 24 | 15 | 24 |
| 15 | **XI** | 25 | 5 | 71 | 12 |
| 16 | **XII** | 32 | 3 | 70 | **38** |
| 17 | **XII** | 0 | 4 | 60 | 26 |
| 18 | **XIII** | 30 | 3 | ∼0[d] | NA |
| 19 | **XIV** | 30 | 7 | 75 | ∼0 |
| 20 | **XIV** | 0 | 40 | 71 | 30 |
| 21 | **XV** | 32 | 1.5 | 79 | ∼0 |
| 22 | **XV** | 0 | 6 | 80 | 17 |
| 23 | **XVI** | 32 | 3 | 82 | 24 |
| 24 | **XVI** | 0 | >72 | 10[e] | ND |

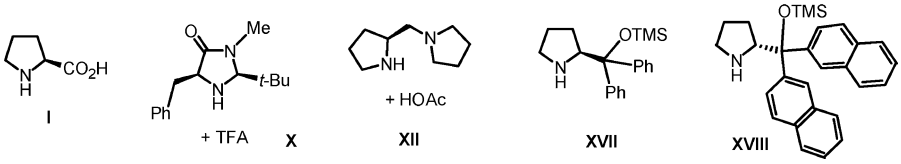
[a] Isolate yield. [b] The enantiomeric excesses (ee) were measured by GC−MS (Shimadzu QP 5000, chiral capillary column, γ-cyclodextrin trifluoroacetyl, Astec Type G-TA, size 30 m × 0.25 mm, flow rate 24 mL/min, temperature range: 60-120 °C, gradient: 3 °C/min). [c] Complex mixtures. [d] Decomposition of crotonaldehydes and recovery of all of **1a**. [e] Self reaction of 3-methyl-2-enal and 50% recovery of crotonaldehyde.

enantioselectivity (41% ee) than at ambient temperature (22% ee; entry 1 in Table 1 and condition A, entry 1, in Table 2). However, at such low temperature, the reaction was too slow to be completed in 2 days. Further lowering of the reaction temperature resulted in difficulty due to the high melting point of $CH_3CN$ (−46 °C). Unfortunately, reaction in other solvents, such as MeOH, THF, DMF, etc., gave either no reaction or much lower yield. Nevertheless, addition of $Et_3N$ to the reaction mixture increased the reaction rate and allowed the reaction to be completed at −40 °C in 20 h, giving 78% ee in 81% yield (condition B, entry 2, Table 2). Other chiral trialkylamines—for example, (−)-sparteine, DHQD, and DHQ—were screened for their efficiency as cocatalyst in the reaction, and (−)-sparteine gave the best results in up to 82% ee at −40 °C (conditions C, D, and E, entries 3−7, Table 2). The reaction attained high enantioselectivity (85%) and up to the maximum of −90% when catalysts **XVII** and **XVIII** were employed[26,27] (conditions F and G, entries 8−10, Table 2). Reaction of MacMillian catalyst (**X**) and the diamine catalyst (**XII**) at lower temperature (−20 and −40 °C), however, gave slow reaction with low enantioselectivity (conditions H and I, entries 11−13, Table 2). These studies implied that the conditions B, C, F,

(26) Recently, the pyrrolidine derivatives, such as diarylprolinol TMS ether, catalysts **XVII** and **XVIII**, have emerged as a promising general enamine organocatalysts. For review, see: Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876.

**TABLE 2. Condition Screening for the Direct Catalytic Asymmetric [4 + 2] Reaction of 3-Methylbut-2-enal (1a) and Crotonaldehyde (2a)[a]**




| entry | condition | *T* (°C) | time (h) | yield[b] % (ee)[c] |
|---|---|---|---|---|
| 1 | A | −20 | 48 | 82 (41) |
| 2 | B | −40 | 20 | 81 (78) |
| 3 | C | −20 | 4 | 82 (62) |
| 4 | C | −40 | 12 | 79 (82) |
| 5 | D | −20 | 12 | 75 (71) |
| 6 | D | −40 | 96 | 65 (70) |
| 7 | E | −20 | 30 | 72 (50) |
| 8 | F | −20 | 96 | 63 (85) |
| 9 | G | 0 | 36 | 68 (−80)[e] |
| 10 | G | −20 | 96 | 72 (−90)[e] |
| 11 | H | −20 | 50 | ∼0[d,f] |
| 12 | I | −20 | 5 | 65 (49) |
| 13 | I | −40 | 10 | 65 (52) |

[a] Condition A: L-proline (50 mol %), $CH_3CN$. Condition B: L-proline (50 mol %), $Et_3N$ (50 mol %), $CH_3CN$. Condition C: L-proline (50 mol %), (−)-sparteine (50 mol %), $CH_3CN$. Condition D: L-proline (50 mol %), DHQD (50 mol %), $CH_3CN$. Condition E: L-proline (50 mol %), DHQ (50 mol %), $CH_3CN$. Condition F: **XVII** (20 mol %), benzoic acid (20 mol %), toluene. Condition G: **XVIII** (20 mol %), benzoic acid (20 mol %), toluene. Condition H: **X** (50 mol %), TFA (50 mol %), $CH_3CN$. Condition I: **XII** (50 mol %), HOAc (50 mol %), $CH_3CN$. [b] Isolated yield. [c] Enantiomeric excess determined by GC−MS (Astec Type G-TA) unless otherwise noted. [d] With complicated mixtures, monitored by NMR. [e] Opposite enantioselectivity was observed. [f] 50% of starting aldehydes remained with complicated mixtures. [g] Enantiomeric excess determined by HPLC (Chiracel OD).

and G were the promising ones for this [4 + 2] cycloaddition. Taking these results into account, a series of the α,β-unsaturated aldehydes were tested under these conditions, and the selected results are summarized in Table 3.

Reaction of 3-methylbut-2-enal and (*E*)-3-formylallyl acetate[28] with L-proline and $Et_3N$ at −20 °C gave 72% yield of **3b** in 45% ee (entry 1, Table 3).[18] The enantioselectivity was nearly doubled when the reaction was conducted at lower temperature (−40 °C, 12 h for completion; entry 2, Table 3). Replacement of $Et_3N$ with (−)-sparteine in the same reaction conditions required 40 h for completion but gave high yield and excellent enantioselectivity (81% yield; 93% ee; entry 3, Table 3). In comparison with the catalysis by L-proline, the reactions catalyzed by **XVII** and **XVIII** were slower, taking 36 h and 4 days for the completion at 0 and −20 °C, respectively (entries 4−6, Table 3).[29]

Reaction of 3-methylbut-2-enal and (*E*)-3-(2-nitrophenyl)-acrylaldehyde with L-proline and $Et_3N$ at ambient temperature gave 60% yield of **3c** in 6% ee (entry 7, Table 3).[30] The enantioselectivity was increased up to 40% ee by lowering the reaction temperature to −20 °C (entries 8 and 9, Table 3). Unfortunately, replacement of $Et_3N$ with (−)-sparteine under the same reaction conditions did not improve enantioselectivity (entry 10, Table 3). Intriguingly, the reaction catalyzed by **XVII** gave 73% yield and 92% ee at ambient temperature, with fast conversion (entry 11, Table 3). However, further lowering of the reaction temperature did not improve the enantioselectivity, affording slow reaction and lower yields (entries 11−13, Table 3). The opposite enantiomer was obtained in good yield and with high enantioselectivity when the reaction was catalyzed by **XVIII** at ambient temperature (entry 14, Table 3). The enantioselectivity was further increased to −99% when the reaction temperature was reduced to −20 °C (entry 15, Table 3).

Reaction of 3-methylbut-2-enal and cinnamaldehyde with L-proline and $Et_3N$ at −20 °C for 24 h gave 78% yield of **3d** in 52% ee (entry 16, Table 3). A slight increase in enantioselectivity was achieved by the replacement of $Et_3N$ with (−)-sparteine under the same reaction conditions (entry 17). Lengthy reactions conducted at −20 °C with catalysts **XVII** and **XVIII** had little effect on the yield of **3d** but markedly improved the enantioselectivities (entries 18−20).

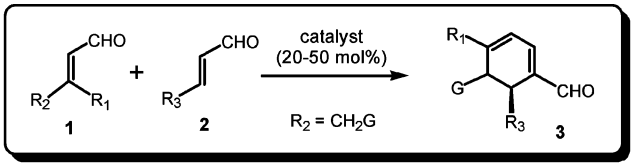
(27) For recent examples of (*S*)-diphenylpyrrolinol silyl ethers as catalysts in organocatalysis, see: (a) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760. (b) Wang, Y.; Liu, X.-F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (c) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804. (d) Marigo, M. T.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (e) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (f) Marigo, M. T.; Wabnitz, C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (g) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922. (h) See ref 17 (xiv).

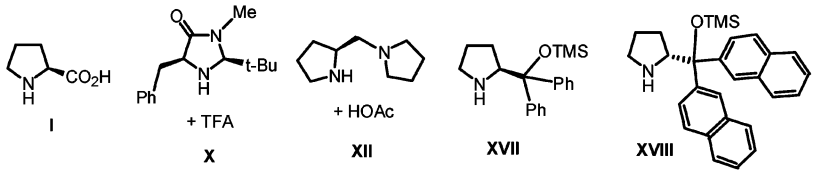
(28) For preparation, see: (a) De La Cruz, A.; He, A.; Thanavaro, A.; Yan, B.; Spilling, C. D.; Rath, N. P. *J. Organomet. Chem.* **2005**, *690*, 2577. (b) James, P.; Felpin, F.-X.; Landais, Y.; Schenk, K. *J. Org. Chem.* **2005**, *70*, 7985. (c) Maruta, Y.; Fukushi, Y.; Ohkawa, K.; Nakanishi, Y.; Tahara, S.; Mizutani, J. *Phytochemistry* **1995**, *38*, 1169.

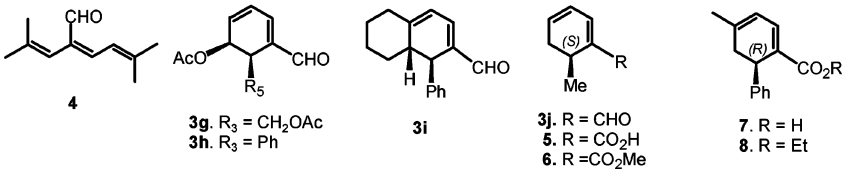
(29) The same reaction at −20 °C in the presence of racemic proline (50 mol %) and (−)-sparteine (50 mol %) gave racemic **3a** in 82% yield (0% ee). No reaction was obtained by the combination of aldehydes with (−)-sparteine alone. A smaller addition of $Et_3N$ resulted in less acceleration of the reaction.

(30) One recrystallization from $EtOAc/CH_2Cl_2$ furnished **3c** in 70% ee.

**TABLE 3. Organocatalysts, Cocatalysts, and Temperature Effects in the [4 + 2] Reactions of α,β-Unsaturated Aldehydes**[a]




| entry | aldehydes | product | condition | *T* (°C) | time (h) | yield[b] % (ee)[c] |
|---|---|---|---|---|---|---|
| 1 | $R_1 = R_2 = Me$; $R_3 = CH_2OAc$ | **3b** | B | −20 | 5 | 72 (45) |
| 2 | $R_1 = R_2 = Me$; $R_3 = CH_2OAc$ | **3b** | B | −40 | 12 | 75 (82) |
| 3 | $R_1 = R_2 = Me$; $R_3 = CH_2OAc$ | **3b** | C | −40 | 40 | 81 (93) |
| 4 | $R_1 = R_2 = Me$; $R_3 = CH_2OAc$ | **3b** | F | 0 | 36 | 65 (72) |
| 5 | $R_1 = R_2 = Me$; $R_3 = CH_2OAc$ | **3b** | F | −20 | 96 | 67 (83) |
| 6 | $R_1 = R_2 = Me$; $R_3 = CH_2OAc$ | **3b** | G | −20 | 96 | 61 (−85)[e] |
| 7 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | B | 25 | 5 | 60 (6)[f] |
| 8 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | B | 0 | 12 | 65 (25)[f] |
| 9 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | B | −20 | 20 | 60 (40)[f] |
| 10 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | C | −20 | 28 | 59 (39) |
| 11 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | F | 25 | 5 | 73 (**92**)[f] |
| 12 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | F | 0 | 8 | 72 (**95**)[f] |
| 13 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | F | −20 | 96 | 53 (**93**)[f] |
| 14 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | G | 25 | 5 | 72 (−**92**)[e,f] |
| 15 | $R_1 = R_2 = Me$; $R_3 = (o\text{-}NO_2)C_6H_4$ | **3c** | G | −20 | 96 | 54 (−**99**)[e,f] |
| 16 | $R_1 = R_2 = Me$; $R_3 = Ph$ | **3d** | B | −20 | 24 | 78 (52) |
| 17 | $R_1 = R_2 = Me$; $R_3 = Ph$ | **3d** | C | −20 | 30 | 72 (57) |
| 18 | $R_1 = R_2 = Me$; $R_3 = Ph$ | **3d** | F | −20 | 96 | 72 (95) |
| 19 | $R_1 = R_2 = Me$; $R_3 = Ph$ | **3d** | G | 0 | 72 | 68 (−82)[e] |
| 20 | $R_1 = R_2 = Me$; $R_3 = Ph$ | **3d** | G | −20 | 96 | 70 (−97)[e] |
| 21 | $R_1 = R_2 = Me$; $R_3 = Et$ | **3e** | B | −40 | 24 | 81 (86) |
| 22 | $R_1 = R_2 = Me$; $R_3 = Et$ | **3e** | C | −40 | 24 | 78 (90) |
| 23 | $R_1 = R_2 = Me$; $R_3 = Et$ | **3e** | F | −20 | 96 | 62 (94) |
| 24 | $R_1 = R_2 = Me$; $R_3 = Et$ | **3e** | G | −20 | 96 | 62 (−85)[e] |
| 25 | $R_1 = R_2 = Me$; $R_3 = i\text{-}Pr$ | **3f** | B | −20 | 24 | 70 (68) |
| 26 | $R_1 = R_2 = Me$; $R_3 = i\text{-}Pr$ | **3f** | C | −40 | 48 | 72 (90) |
| 27 | $R_1 = R_2 = Me$; $R_3 = i\text{-}Pr$ | **3f** | F | 25 | 5 | 16 (97)[g] |
| 28 | $R_1 = R_2 = Me$; $R_3 = i\text{-}Pr$ | **3f** | F | −20 | 96 | 13 (**98**)[g] |
| 29 | $R_1 = R_2 = Me$; $R_3 = i\text{-}Pr$ | **3f** | G | −20 | 96 | 14 (−**98**)[e,g] |
| 30 | $R_1 = H$; $R_2 = R_3 = CH_2OAc$ | **3g** | B | −20 | 8 | 70 (**95**) |
| 31 | $R_1 = H$; $R_2 = R_3 = CH_2OAc$ | **3g** | C | −20 | 12 | 65 (69) |
| 32 | $R_1 = H$; $R_2 = R_3 = CH_2OAc$ | **3g** | F | −20 | 96 | ∼0[d] |
| 33 | $R_1 = H$; $R_2 = R_3 = CH_2OAc$ | **3g** | G | −20 | 96 | ∼0[d] |
| 34 | $R_1 = H$; $R_2 = CH_2OAc$; $R_3 = Ph$ | **3h** | B | −20 | 5 | 63 (77) |
| 35 | $R_1 = H$; $R_2 = CH_2OAc$; $R_3 = Ph$ | **3h** | C | −20 | 10 | 59 (70) |
| 36 | $R_1 = H$; $R_2 = CH_2OAc$; $R_3 = Ph$ | **3h** | F | 25 | 5 | ∼0[h] |
| 37 | $R_1 = H$; $R_2 = CH_2OAc$; $R_3 = Ph$ | **3h** | G | 25 | 5 | ∼0[h] |
| 38 | $R_1 = R_2 = -(CH_2)_5-$; $R_3 = Ph$ | **3i** | A | 25 | 4 | 84 (7:1 dr); (1)[i] |
| 39 | $R_1 = R_2 = -(CH_2)_5-$; $R_3 = Ph$ | **3i** | A | 0 | 72 | 85 (34:1 dr); (7)[i] |
| 40 | $R_1 = R_2 = -(CH_2)_5-$; $R_3 = Ph$ | **3i** | F | 25 | 5 | 63 (100:0 dr); (98)[i] |
| 41 | $R_1 = R_2 = -(CH_2)_5-$; $R_3 = Ph$ | **3i** | F | −20 | 96 | 45 (100:0 dr); (>99.5)[i] |
| 42 | $R_1 = R_2 = -(CH_2)_5-$; $R_3 = Ph$ | **3i** | G | 25 | 5 | 64 (100:0 dr); (−95)[e,i] |
| 43 | $R_1 = R_2 = -(CH_2)_5-$; $R_3 = Ph$ | **3i** | G | −20 | 96 | 46 (100:0 dr); (>−99)[e,i] |
| 44 | $R_1 = H$; $R_2 = R_3 = Me$ | tolualdehyde/**3j** (64:36) | A | reflux | 4 | 76 (10) |
| 45 | $R_1 = H$; $R_2 = R_3 = Me$ | tolualdehyde/**3j** | B | reflux | 2 | ∼0[d] |
| 46 | $R_1 = H$; $R_2 = R_3 = Me$ | tolualdehyde/**3j** (40:60) | B | 35 | 2 | 81 (16) |
| 47 | $R_1 = H$; $R_2 = R_3 = Me$ | tolualdehyde/**3j** (50:50) | B | 0 | 10 | 80 (14) |
| 48 | $R_1 = H$; $R_2 = R_3 = Me$ | tolualdehyde/**3j** | F | −20 | 96 | ∼0[d] |
| 49 | $R_1 = H$; $R_2 = R_3 = Me$ | tolualdehyde/**3j** | G | 25 | 3 | ∼0[d] |
| 50 | $R_1 = H$; $R_2 = R_3 = Me$ | tolualdehyde/**3j** (10:90) | J | reflux | 18 | 79 (12) |

[a] Condition A: L-proline (50 mol %), $CH_3CN$. Condition B: L-proline (50 mol %), $Et_3N$ (50 mol %), $CH_3CN$. Condition C: L-proline (50 mol %), (−)-sparteine (50 mol %), $CH_3CN$. Condition F: **XVII** (20 mol %), benzoic acid (20 mol %), toluene. Condition G: **XVIII** (20 mol %), benzoic acid (20 mol %), toluene. Condition J: 4-hydroxyproline (20 mol %), $CH_3CN$. [b] Isolated yield. [c] Enantiomeric excess determined by GC−MS (Astec Type G-TA) unless otherwise addressed. [d] With complicated mixtures, monitored by NMR. [e] Opposite enantioselectivity was observed. [f] Enantiomeric excess determined by HPLC (Chiracel OD). [g] More than 40% of the aldol product **4** was obtained. [h] Reaction at −20 °C for 96 h gave the same results, decomposition of (*E*)-3-formylallyl acetate, recovered cinnamaldehyde. [i] Absolute stereochemistry not determined.

Reaction of 3-methylbut-2-enal and pent-2-enal with L-proline and $Et_3N$ at −40 °C for 24 h gave 81% yield of **3e** in 86% ee (entry 21, Table 3). The enantioselectivity was increased slightly to 90% by the replacement of $Et_3N$ with (−)-sparteine under the same reaction conditions (entry 22, Table 3). The reactions catalyzed by **XVII** and **XVIII** at −20 °C for 4 days gave 62% yield of **3e** in 94 and −85% ee, respectively (entries 23 and 24, Table 3).

Reaction of 3-methylbut-2-enal and 4-methyl-pent-2-enal with L-proline and $Et_3N$ at −20 °C for 24 h gave 70% yield of **3f** in 68% ee (entry 25, Table 3). The enantioselectivity was increased dramatically to 90% by the replacement of $Et_3N$ with (−)-sparteine at −40 °C (entry 26, Table 3). The catalysts **XVII** and **XVIII** afforded low yields of **3f** but high enantioselectivities (98% ee), along with the Baylis−Hillman side products **4** (entries 27−29, Table 3).

Self-condensation of (*E*)-3-formylallyl acetate with L-proline and $Et_3N$ at −20 °C gave 70% yield of **3g** in 95% ee (entry 30, Table 3). Unfortunately, replacement of $Et_3N$ with (−)-sparteine decreased the enantioselectivity to 69%, while the reaction catalyzed by **XVII** and **XVIII** gave no observable **3g** but rather complicated mixtures of products (entries 31−33, Table 3).

Reaction of (*E*)-3-formylallyl acetate and cinnamaldehyde with L-proline and $Et_3N$ at −20 °C was fast, completed in 5 h, with 63% yield of **3h** in 77% ee (entry 34, Table 3). Replacement of $Et_3N$ with (−)-sparteine under the same reaction conditions, however, did not improve the enantioselectivity (entry 35, Table 3). Unfortunately, the reaction catalyzed by **XVII** and **XVIII** gave virtually no **3h** but the decomposition of (*E*)-3-formylallyl acetate and recovered cinnamaldehyde (entries 36 and 37, Table 3).

Reaction of cyclohexylidene acetaldehyde and cinnamaldehyde with L-proline at ambient temperature for 4 h gave 84% yield of **3i** in 7:1 diastereomeric ratio and almost no enantioselectivity. The diastereomeric ratio of the reaction was increased to 34:1 at 0 °C (entries 38 and 39, Table 3). Both the diastereomeric ratio and the enantioselectivity of the reaction were increased to >99% when catalyzed by **XVII** and **XVIII** at −20 °C for 4 days (entries 40−43, Table 3).

Recently, we have reported the observation of [3 + 3] cycloaddition adducts in the self-condensation of crotonaldehyde with L-proline at low temperature.[16a] Addition of $Et_3N$ to the reaction mixture increased the ratio of [4 + 2] versus [3 + 3] adduct and attained a maximum of 1:1 in $CH_3CN$ (entries 44−47, Table 3).[31] The reaction catalyzed by **XVII** or **XVIII** gave complicated mixtures with no observed [4 + 2] adduct (entries 48 and 49, Table 3). Interestingly, the reaction catalyzed by 4-hydroxyproline in refluxing $CH_3CN$ gave the [4 + 2] adduct as the major product (entry 50, Table 3).

We draw the following conclusions from the results in Table 2 and 3: (1) Reactions at lower temperature gave better enantioselectivity of the product than reactions at higher temperature. $Et_3N$ plays a role in facilitating the reaction and allows the reaction to proceed at lower temperature and, in return, affords better enantioselectivity of the products. (2) In many cases, the reactions catalyzed by L-proline/(−)-sparteine provided better enantioselectivity than those reactions catalyzed by L-proline/$Et_3N$. (3) For the reaction of aldehyde **1** with $\beta$-dialkyl substituents, **XVII** and **XVIII** gave better enantioselectivity and in some cases gave >99% ee. However, if both of the two reactants were monoalkylunsaturated aldehydes, the reactions catalyzed by **XVII** and **XVIII** yielded complicated mixtures. (4) Although 4-hydroxyproline was a poor catalyst in the reaction of **1** and **2**, it was the best catalyst as the [4 + 2] promoter in the self-condensation of crotonaldehyde. (5) For cross-annulation, such as in the mixtures of $\beta$-dialkyl- and $\beta$-monounsaturated aldehydes, such as **1** and **2**, the $\beta$-dialkylunsaturated aldehyde served as the donor in the dienamine Michael reaction step for attacking the monoalkylunsaturated aldehyde acceptor, rather than self-condensation or being attacked by the monoalkyl counterpart. (6) Shorter reaction times were obtained by raising the reaction temperature, but this condition also decreased the enantioselectivity.

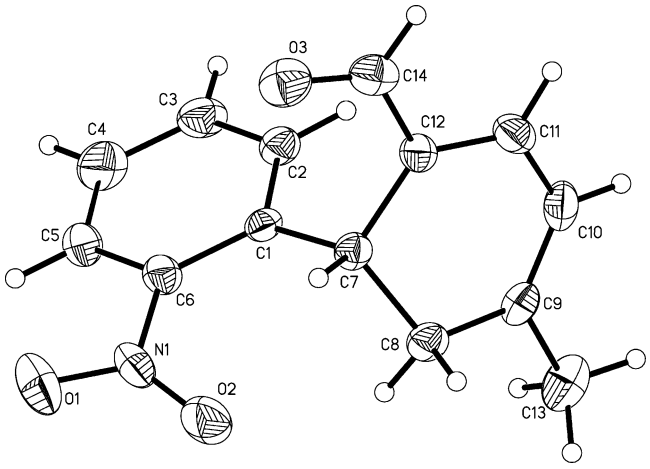



**FIGURE 1.** ORTEP plot for X-ray crystal structure of **3c**.

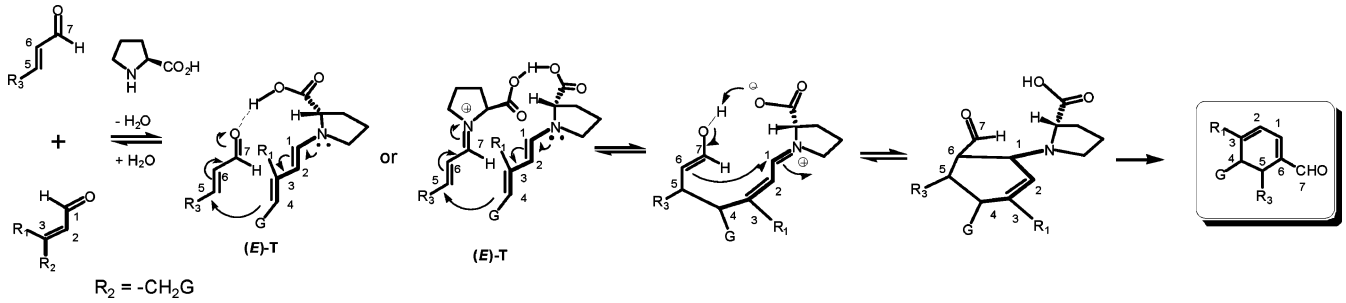
**2. Structure and Stereochemistry Elucidation in the Formal [4 + 2] Adducts.** The structure of **3c** was assigned unambiguously by its single-crystal X-ray analysis (Figure 1).[18,32] The formation of the [4 + 2] adduct may be produced through a stepwise cascade reaction and equilibrium process as shown in Scheme 1. It is likely that the proline-catalyzed Michael reaction of $\alpha,\beta$-unsaturated aldehyde proceeds via transition state (*E*)-T, followed by an indirect Mannich reaction (iminium-ion-activating) pathway to afford the adducts. The mechanism also explains the chemoselectivity in the cross-annulation: the $\beta$-dialkyl-$\alpha,\beta$-unsaturated aldehydes, such as **1**, are more easily enolized, providing the corresponding dienamine, followed by their attacking the $\beta$-monoalkyl-$\alpha,\beta$-unsaturated aldehydes, such as compound **2**. Recently, several examples of organocatalysis have been observed to have better yields in the presence of water.[33] The current reactions are not particularly sensitive to moisture or air. However, addition of water to the reaction mixture reduced the reaction rate dramati-

(31) **3j** is very volatile and is easily sublimated; it is necessary to evaporate with caution.

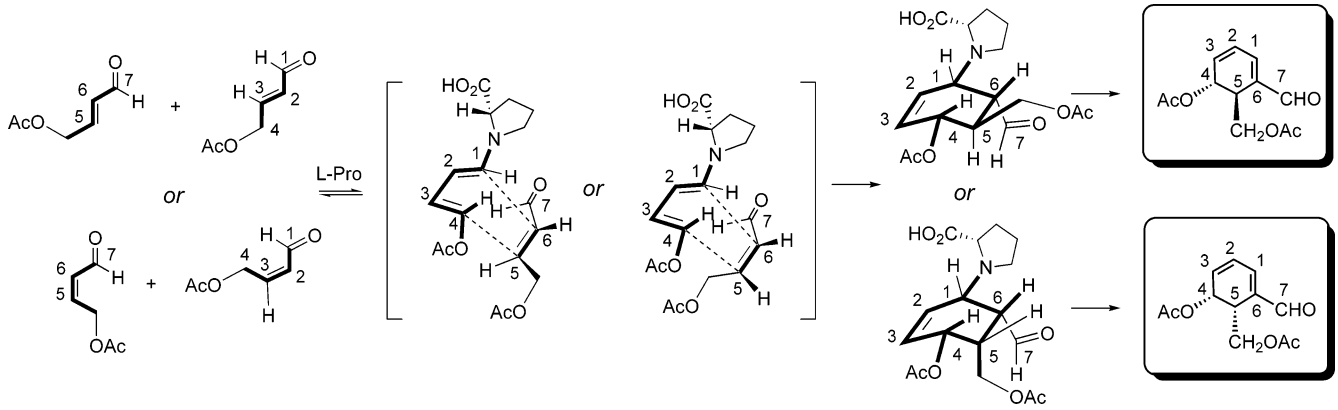
(32) Crystallographic data for **3c**: $C_{14}H_{13}NO_3$, $M = 243.25$, orthorhombic, space group *Pbca*, $T = 294$ K, $a = 8.4574(13)$, $b = 15.167(2)$, $c = 19.340(3)$ Å, $V = 2480.8(6)$ Å$^3$, $Z = 8$, $D = 1.303$ g/cm$^3$, $\lambda$ (Mo K$\alpha$) = 0.71073 Å, 20 391 reflections collected, 3026 unique reflections, 165 parameters refined on $F^2$, $R = 0.1066$, $wR2[F^2] = 0.1847$ [1251 data with $F^2 > 2\sigma(F^2)$].

(33) For recent advances and debates in the study of organocatalysis "on water" and "in the presence of water", see: (a) Hayashi, Y. *Angew. Chem, Int. Ed.* **2006**, *45*, 8103. (b) Brogan, A. P.; Dickerson, T. J.; Janda, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 8100. (c) Gonzalez-Cruz, D.; Tejedor, D.; de Armas, P.; Morales, E. Q.; Garcia-Tellado, F. *Chem. Commun.* **2006**, 2798. (d) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734. (e) Guizzetti, S.; Benaglia, M.; Raimondi, L.; Celentano, G. *Org. Lett.* **2007**, *9*, 1247.

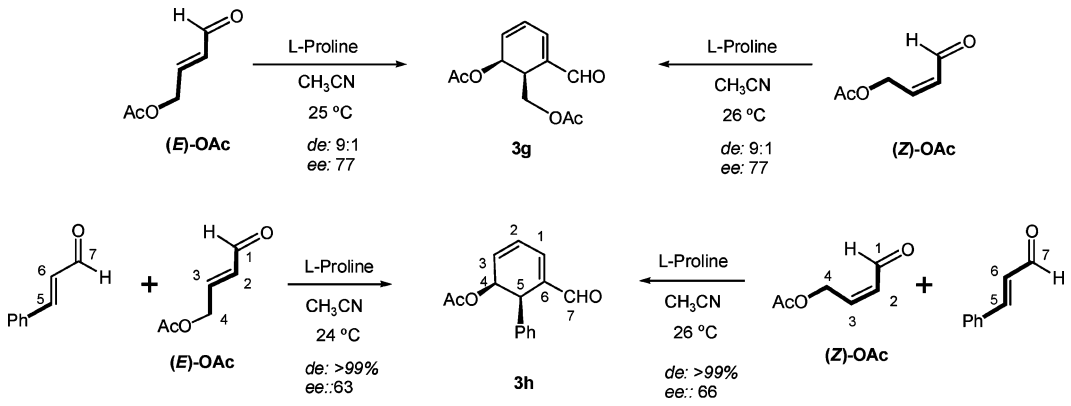
**SCHEME 1. Proposed Mechanism for the Formation of [4 + 2] Adduct via Dienamine Catalyzing Michael Reaction**



**SCHEME 2. Proposed Mechanism for the Formation of [4 + 2] Adduct via Dienamine-Catalyzed Diels−Alder Reaction**



**SCHEME 3. Reactions of (*E*)-3-Formylallyl Acetate and (*Z*)-3-Formylallyl Acetate**



cally. This was probably due to the fact that excess water drives the reverse reaction in the equilibrium process for the formation of the dienamine. Another possible mechanism for the formation of the [4 + 2] adducts could be via the Diels−Alder reaction (Scheme 2). Unlike the well-documented examples in facilitating Mannich reactions,[34] the trialkylamines rarely accelerate the Diels−Alder reaction.[35]

A few experiments have been conducted to shed some light on the reaction mechanism. Self-dimerization of (*Z*)-4-acetoxycrotonaldehyde[36] and (*E*)-4-acetoxycrotonaldehyde, individually, gave the same adduct **3g** with the same diastereoselectivity (favoring *cis* in 80% de) and enantioselectivity (77%) (Scheme 3). Similar results were observed for the cross-[4 + 2]-reaction of (*E*)-4-acetoxycrotonaldehyde and (*Z*)-4-acetoxycrotonaldehyde with cinnamaldehyde, affording **3h** with >99% de, 63% ee and >99% de, 66% ee, respectively (Scheme 3).

Typically, with only a few exceptions, the iminium-catalyzed intermolecular Diels−Alder reaction favored *endo*-selectivity due to secondary orbital effects, as depicted in Scheme 2. Diels−Alder reaction of the dienamine and α,β-unsaturated aldehyde via the *endo*-transition state would lead to the formation of the *trans*- or *cis*-diene aldehyde depending on the geometry of the starting compounds, while the reactions we observed afforded *cis*-adducts preferentially (90 to ∼100%).[37] The *cis*-selectivity and the same enantioselectivity for the formation of adducts **3g**

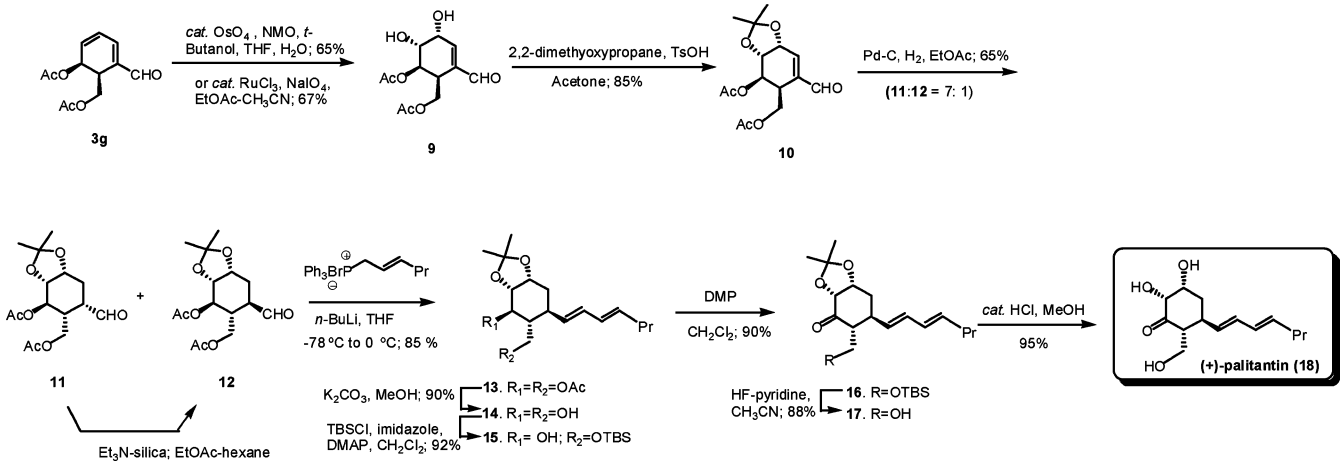
(34) For recent studies on the organocatalytic Mannich reactions with trialkylamines, see: Fu, A.; List, B.; Thiel, W. *J. Org. Chem.* **2006**, *71*, 320.

(35) For the combination of $Et_3N$ and Lewis acid (LiCl) leading to synergistic catalysis of the Diels−Alder reaction of anthrone with methylcrotonate, see: Harrison, R.; Rickborn, B. *Org. Lett.* **2002**, *4*, 1711.

(36) For the preparation, see: Inhoffen, H. H.; Heimann-Trosien, J.; Muxfeldt, H.; Kramer, H. *Chem. Ber.* **1957**, *90*, 187.

(37) (a) For recent developments in the *exo*-selective binaphthyl-derived diamine catalysis, see: Kano, T.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2006**, *8*, 2687. (b) For the *exo*-selective camphor-derived hydrazine catalyst, see: Lemay, M.; Aumand, L.; Ogilvie, W. W. *Adv. Synth. Catal.* **2007**, *349*, 441.

**SCHEME 4. Total Synthesis of (+)-Palitantin from the [4 + 2] Adduct 3g**




and **3h** suggested that the reaction likely proceeded through a dieniminium−enamine mechanism (dienamine and iminium-ion-activating Michael reaction)[38,39] rather than via the dienamine Diels−Alder reaction (accelerated by the formation of the α,β-unsaturated iminium).[40]

Chlorite oxidation of **3j** to **5** ($NaClO_2$, *t*-BuOH, 2-methyl-2-butene, $NaH_2PO_4$, 25 °C; 76%), followed by esterification ($CH_2N_2$ in $Et_2O$, 25 °C), afforded (−)-**6** in 75% yield. The enantiomer, (+)-**6**, has been used for the synthesis of (−)-pumiliotoxin C,[41] and this result disclosed the absolute stereochemistry of **3j** to be *sinistrus* as depicted in the structures in Table 3. Chlorite oxidation of (−)-**3d** to (−)-**7** ($NaClO_2$, *t*-BuOH, 2-methyl-2-butene, $NaH_2PO_4$, 25 °C; 80%), followed by esterification (EtOH, cat. $H_2SO_4$, 25 °C), afforded (−)-**8** in 85% yield. The absolute stereochemistry of (−)-**8** has been reported,[42] and the absolute stereochemistry of **3d** was determined to be that as shown in the structures in Table 3.

**3. Applications of the Formal [4 + 2] Adducts in the Total Synthesis of (+)-Palitantin.** We envisioned diacetate **3g** would be a versatile synthon for other synthetically valuable building blocks. To demonstrate the synthetic potential of this reaction, diacetate **3g** was transferred to (+)-palitantin, a polyketide metabolite isolated from the *Penicillium palitans*[43] and *Penicillium brefeldianum*,[44] having antifungal activity[45] and antibiotic activity[46] as well as being an HIV-1 integrase inhibitor[47] (Scheme 4). To date, one racemic[48] and a few asymmetric syntheses of palitantin or its enantiomer have been reported.[49] Our approach started from the dihydroxylation of **3g** to diol **9** ($OsO_4$, NMO, *t*-BuOH−THF−$H_2O$; 65%) followed by protection of the diol ($Me_2C(OMe)_2$, acetone, cat. *p*-TsOH; 85%), affording acetonide **10**. Hydrogenation of the alkene **10** afforded the aldehydes **11** and **12** in a ratio of 7 to 1. An unusual isomerization of the *cis*-acetoxy and acetoxymethyl group toward the *trans*-product was observed during the hydrogenation process. The *trans*-product arose probably due to the double-bond isomerization by the allylic hydrogen exchange (via π-allyl intermediate) that accompanies hydrogenation.[50] **11** was unstable during the purification by silica gel flash chromatography, and some of the **11** gradually isomerized to **12**. The process was facilitated by the addition of 1% $Et_3N$ in the eluent (EtOAc/hexane) during the purification of **11** by silica gel flash chromatography to give **12**. Wittig reaction of aldehyde **12** with (2*E*)-hexenyl triphenylphosphonium bromide[51] provided dienes **13**, along with the *Z*-isomer (*Z*)-**13** in a ratio of 3:1 and 85% yield. Hydrolysis of acetate **13** ($K_2CO_3$, MeOH; 90%), followed by protection of **14** (TBSCl, imidazole, DMAP, $CH_2Cl_2$; 92%), afforded **15**. Oxidation of alcohol **15** by Dess−Martin periodinane (DMP, $CH_2Cl_2$; 90%), followed by deprotection of TBS ether **16** (HF/pyridine, $CH_3CN$; 88%), provided the acetonide **17**.[52] Deprotection of acetonide **17** (cat. HCl−MeOH) afforded

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(+)-palitantin in 95% yield. Optical rotation data obtained from **17** and **18** obtained also verified the absolute stereochemistry of **3g**.

## Conclusion

We have observed that the use of trialkylamines as cocatalysts for the formal [4 + 2] reaction has a profound and appreciable effect on both the yield and reaction rate of the reaction. The methodology allows the reaction to proceed at low temperature and yields the products with much higher enantioselectivity than the products obtained at ambient temperature. Furthermore, some reactions were achieved with the catalysis of diarylprolinol TMS ether and afforded high enantioselectivity (>99% ee). The structure of the [4 + 2] adduct produced from 3-methylbut-2-enal and (*E*)-3-(2-nitrophenyl)acrylaldehyde was elucidated unambiguously from the single-crystal X-ray analysis. The absolute configuration of some [4 + 2] adducts was determined by sequential transformation of the adducts to natural compounds and comparison with the literature. Synthetic application was successful in achieving the total synthesis of (+)-palitantin.

## Experimental Section

**Typical Procedure, Methods in Table 2, Preparation of 4,6-Dimethylcyclohexa-1,3-dienecarbaldehyde (3a). Method A:** To a solution of crotonaldehyde (210 mg, 3.0 mmol) and 3-methylbut-2-enal (252 mg, 3.0 mmol) in $CH_3CN$ (15 mL) was added L-(−)-proline (172 mg, 1.5 mmol) for 48 h at −20 °C until the reaction was completed, monitored by TLC. To the solution was added $H_2O$ (10 mL), and extracted with EtOAc (30 mL × 2). The organic solution was washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.50 in 5% EtOAc/hexane) to give **3a** (334 mg; 82% yield) as a colorless oil. **Method B:** To a solution of crotonaldehyde (210 mg, 3.0 mmol) and 3-methylbut-2-enal (252 mg, 3.0 mmol) in $CH_3CN$ (15 mL) were added L-(−)-proline (172 mg, 1.5 mmol) and $Et_3N$ (150 mg, 1.5 mmol). The solution was stirred for 20 h at −40 °C until the reaction was completed, monitored by TLC. To the solution was added $H_2O$ (10 mL), and extracted with EtOAc (30 mL × 2). The organic solution was washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.50 in 5% EtOAc/hexane) to give **3a** (330 mg; 81% yield) as a colorless oil. **Method C:** To a solution of crotonaldehyde (210 mg, 3.0 mmol) and 3-methylbut-2-enal (252 mg, 3.0 mmol) in $CH_3CN$ (15 mL) were added L-(−)-proline (172 mg, 1.5 mmol) and (−)-sparteine (350 mg, 1.5 mmol). The solution was stirred for 4 h at −20 °C until the reaction was completed, monitored by TLC. To the solution was added $H_2O$ (10 mL), and extracted with EtOAc (30 mL × 2). The organic solution was washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.50 in 5% EtOAc/hexane) to give **3a** (334 mg; 82% yield) as a colorless oil. **Method D:** To a solution of crotonaldehyde (7 mg, 0.1 mmol) and 3-methylbut-2-enal (8.4 mg, 0.1 mmol) in $CH_3CN$ (1 mL) were added L-(−)-proline (6 mg, 0.05 mmol) and $(DHQD)_2PHAL$ (39 mg, 0.05 mmol). The solution was stirred for 12 h at −20 °C until the reaction was completed, monitored by TLC. To the solution was added $H_2O$ (10 mL), and extracted with EtOAc (30 mL × 2). The organic solution was washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.50 in 5% EtOAc/hexane) to give **3a** (10.2 mg; 75% yield) as a colorless oil. **Method E:** To a solution of crotonaldehyde (7 mg, 0.1 mmol) and 3-methylbut-2-enal (8.4 mg, 0.1 mmol) in $CH_3CN$ (1 mL) were added L-(−)-proline (6 mg, 0.05 mmol) and $(DHQ)_2PHAL$ (39 mg, 0.05 mmol). The solution was stirred for 30 h at −20 °C until the reaction was completed, monitored by TLC. To the solution was added $H_2O$ (10 mL), and extracted with EtOAc (30 mL × 2). The organic solution was washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.50 in 5% EtOAc/hexane) to give **3a** (9.8 mg; 72% yield) as a colorless oil. **Method F:** To a solution of crotonaldehyde (35 mg, 0.5 mmol) and 3-methylbut-2-enal (42 mg, 0.5 mmol) in toluene (1 mL) were added (*S*)-(diphenyltrimethylsiloxymethyl)pyrrolidine (**XVII**) (33 mg, 0.1 mmol) and benzoic acid (12 mg, 0.1 mmol). The solution was stirred for 96 h at −20 °C until the reaction was completed, monitored by TLC. To the solution was added $H_2O$ (3 mL), and extracted with EtOAc (10 mL × 2). The organic solution was washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.50 in 5% EtOAc/hexane) to give **3a** (42.8 mg; 63% yield) as a colorless oil. **Method G:** To a solution of crotonaldehyde (35 mg, 0.5 mmol) and 3-methylbut-2-enal (42 mg, 0.5 mmol) in toluene (1 mL) were added (*R*)-2-{dinaphthalen-2-yl[(trimethylsilanyl)oxy]methyl}pyrrolidine (**XVIII**) (42 mg, 0.1 mmol) and benzoic acid (12 mg, 0.1 mmol). The solution was stirred for 36 h at 0 °C until the reaction was completed, monitored by TLC. To the solution was added $H_2O$ (3 mL), and extracted with EtOAc (10 mL × 2). The organic solution was washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.50 in 5% EtOAc/hexane) to give **3a** (42.8 mg; 63% yield) as a colorless oil. **Method I:** To a solution of crotonaldehyde (35 mg, 0.5 mmol) and 3-methylbut-2-enal (42 mg, 0.5 mmol) in $CH_3N$ (2.5 mL) were added (*S*)-(+)-(2-pyrrolidinylmethyl)pyrrolidine (**XII**) (39 mg, 0.25 mmol) and HOAc (15 mg, 0.25 mmol). The solution was stirred for 5 h at −20 °C until the reaction was completed, monitored by TLC. To the solution was added $H_2O$ (3 mL), and extracted with EtOAc (10 mL × 2). The organic solution was washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.50 in 5% EtOAc/hexane) to give **3a** (44.2 mg; 65% yield) as a colorless oil. GC−MS analysis, with chiral column: γ-cyclodextrin trifluoroacetyl 50 m × 0.25 mm, 60−120 °C, 2 °C/min; (*S*)-**3a**: $t_r$ = 33.4 min, (*R*)-**3a**: $t_r$ = 35.8 min.

**4,6-Dimethylcyclohexa-1,3-dienecarbaldehyde (3a):** $R_f$ = 0.50 in 5% EtOAc/hexane; 41% ee; $[\alpha]^{20}_D = -5.7$ (*c* 4.5, $CHCl_3$); IR (neat) 2925, 1685, 1255, 805, 738 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) δ 9.39 (s, 1 H), 6.63 (d, *J* = 5.5 Hz, 1 H), 5.90−5.92 (m, 1 H), 2.82−2.86 (m, 1 H), 2.46 (dd, *J* = 18.0, 9.0 Hz, 1 H), 1.97 (d, *J* = 18.0 Hz, 1 H), 1.87 (s, 3 H), 0.88 (d, *J* = 7.0 Hz, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) δ 192.4 (CH), 147.0 (C), 143.0 (CH), 140.1 (C), 118.6 (CH), 36.4 ($CH_2$), 24.4 ($CH_3$), 23.7 (CH), 18.0 ($CH_3$); MS (*m*/*z*, relative intensity) 136 ($M^+$, 43), 121 (22), 107 (68), 93 (58), 91 (100), 77 (61); exact mass calcd for $C_9H_{12}O$ ($M^+$) 136.0888; found 136.0885.

**Acetic Acid 2-Formyl-5-methylcyclohexa-2,4-dienylmethyl ester (3b):** $R_f$ 0.50 in 30% EtOAc/hexane; 83% ee; $[\alpha]^{22} = -43.6$ (*c* 3.3, $CHCl_3$); IR (neat) 1739, 1670, 1577, 1237, 1036, 808, 740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) δ 9.45 (s, 1 H), 6.81 (d, *J* = 6.0 Hz, 1 H), 5.97−5.94 (m, 1 H), 3.96 (dd, *J* = 10.5, 9.5 Hz, 1

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H), 3.80 (dd, $J$ = 10.5, 5.5 Hz, 1 H), 3.20−3.10 (m, 1 H), 2.44−2.38 (m, 1 H), 2.40 (d, $J$ = 9.0 Hz, 1 H), 2.01 (s, 3H), 1.90 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 191.9 (CH), 171.2 (C), 147.6 (C), 145.4 (CH), 134.3 (C), 119.0 (CH), 63.2 ($CH_2$), 31.1 ($CH_2$), 28.6 (CH), 24.1 ($CH_3$), 20.9 ($CH_3$); MS (*m*/*z*, relative intensity) 194 ($M^+$, 3), 191 (15), 185 (7), 163 (16), 149 (53), 121 (42), 107 (34); exact mass calcd for $C_{11}H_{14}O_3$ ($M^+$) 194.0943; found 194.0943.

**4-Methyl-6-(2-nitrophenyl)cyclohexa-1,3-dienecarbaldehyde (3c):** $R_f$ 0.50 in 30% EtOAc/hexane; 93% ee; $[\alpha]^{22}_D = -195.5$ (*c* 5.3, $CHCl_3$); IR (neat) 12960, 1670, 1581, 1523, 1352, 1261, 1197, 804 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.44 (s, 1 H), 7.86−7.84 (m, 1 H), 7.43−7.40 (m, 1 H), 7.33−7.31 (m, 1 H), 7.30−7.24 (m, 1 H), 7.09−7.07 (m, 1 H), 6.08 (br s, 1 H), 4.60 (d, $J$ = 11.5 Hz, 1 H), 3.01−2.94 (m, 1 H), 2.49 (d, $J$ = 19.0 Hz, 1 H), 1.84(s, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 191.4 (CH), 148.7 (C), 147.5 (C), 145.2 (CH), 137.2 (C), 135.8 (C), 132.8 (CH), 128.9 (CH), 127.4 (CH), 124.8 (CH), 118.9 (CH), 36.7 ($CH_2$), 29.5 (CH), 24.1 ($CH_3$); MS (*m*/*z*, relative intensity) 243 ($M^+$, 1), 225 (1), 195 (100), 180 (48), 165 (48), 152 (39); exact mass calcd for $C_{14}H_{13}NO_3$ ($M^+$) 243.0895; found 243.0896.

**4-Methyl-6-phenylcyclohexa-1,3-dienecarbaldehyde (3d):** $R_f$ 0.70 in 10% EtOAc/hexane; 95% ee; $[\alpha]^{22}_D = -230.1$ (*c* 6.0, $CHCl_3$); IR (neat) 2924, 1670, 1577, 1195, 792, 755, 699 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.49 (s, 1 H), 7.17−7.24 (m, 4 H), 7.14−7.16 (m, 1 H), 6.90 (d, $J$ = 5.5 Hz, 1 H), 6.02−6.05 (m, 1 H), 4.06 (d, $J$ = 9.5 Hz, 1 H), 2.80−2.87 (m, 1 H), 2.44 (dd, $J$ = 18.5, 0.5 Hz, 1 H), 1.86 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 191.9 (CH), 147.1 (C), 144.0 (CH), 143.0 (C), 137.1 (C), 128.2 (two CH), 126.8 (two CH), 126.5 (CH), 119.3 (CH), 36.8 ($CH_2$), 34.0 (CH), 24.0 ($CH_3$); MS (*m*/*z*, relative intensity) 198 ($M^+$, 72), 183 (47), 169 (100), 154 (62), 91 (83), 77 (59); exact mass calcd for $C_{14}H_{14}O$ ($M^+$) 198.1045; found 198.1042.

**6-Ethyl-4-methylcyclohexa-1,3-dienecarbaldehyde (3e):** $R_f$ 0.50 in 5% EtOAc/hexane; 94% ee; $[\alpha]^{22}_D = -41.7$ (*c* 1.0, $CHCl_3$); IR (neat) 3019, 2925, 2858, 1688, 1459, 1216, 759 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.43 (s, 1 H), 6.68 (d, $J$ = 5.5 Hz, 1 H), 5.92−5.90 (m, 1 H), 2.67−2.73 (m, 1 H), 2.37−2.43 (m, 1 H), 2.18 (d, $J$ = 18.0 Hz, 1 H), 1.89 (s, 3 H), 1.20−1.40 (m, 2 H), 0.82 (t, $J$ = 7.5 Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 192.7 (CH), 147.5 (C), 143.9 (CH), 139.4 (C), 119.0 (CH), 33.2 ($CH_2$), 30.2 (CH), 24.7 ($CH_2$), 24.3 ($CH_3$), 11.0 ($CH_3$); MS (*m*/*z*, relative intensity) 150 ($M^+$, 22), 121 (23), 93 (100), 77 (58); exact mass calcd for $C_{10}H_{14}O$ ($M^+$) 150.1045; found 150.1042.

**6-Isopropyl-4-methylcyclohexa-1,3-dienecarbaldehyde (3f):** $R_f$ 0.50 in 5% EtOAc/hexane; 98% ee; $[\alpha]^{22}_D = -27.1$ (*c* 1.3, $CHCl_3$); IR (neat) 2924, 1671, 1577, 1456, 1200, 799, 750 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.44 (s, 1 H), 6.73 (d, $J$ = 5.5 Hz, 1 H), 5.85−5.87 (m, 1 H), 2.63 (dd, $J$ = 9.5, 6.0 Hz, 1 H), 2.35 (dd, $J$ = 9.5, 18.0 Hz, 1 H), 2.25 (d, $J$ = 18.0 Hz, 1 H), 1.86 (s, 3 H), 1.72−1.77 (m, 1 H), 0.82 (d, $J$ = 7.0 Hz, 3 H), 0.76 (d, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 193.0 (CH), 148.3 (C), 144.9 (CH), 138.2 (C), 119.2 (CH), 34.7 (CH), 30.9 ($CH_2$), 30.2 (CH), 23.9 ($CH_3$), 20.3 ($CH_3$), 18.7 ($CH_3$); MS (*m*/*z*, relative intensity) 164 ($M^+$, 10), 121 (31), 120 (19), 119 (36), 107 (14), 93 (100), 77 (53); exact mass calcd for $C_{11}H_{16}O$ ($M^+$) 164.1201; found 164.1199.

**5-Methyl-2-(2-methylpropenyl)hexa-2,4-dienal (4):** $R_f$ 0.60 in 17% EtOAc/hexane; IR (neat) 2925, 2860, 1678, 1628, 1444, 1379, 1227, 1173, 1134, 850 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.45 (s, 1 H), 7.09 (d, $J$ = 12.0 Hz, 1 H), 6.11 (d, $J$ = 12.0 Hz, 1 H), 5.74 (br s, 1 H), 1.95 (s, 3 H), 1.93 (s, 3 H), 1.88 (s, 3 H), 1.49 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 194.6 (CH), 148.2 (C), 145.0 (CH), 140.0 (C), 137.0 (C), 122.9 (CH), 116.1 (CH), 27.2 ($CH_3$), 25.9 ($CH_3$), 20.4 ($CH_3$), 19.2 ($CH_3$); MS (*m*/*z*, relative intensity) 165 ($M^+ + 1$, 44), 152 (23), 135 (23), 105 (36), 69 (64), 57 (100); exact mass calcd for $C_{11}H_{16}O$ ($M^+$) 164.1201; found 164.1209.

**Acetic Acid 6-Acetoxy-2-formylcyclohexa-2,4-dienylmethyl ester (3g):** $R_f$ 0.50 in 50% EtOAc/hexane; $[\alpha]^{20}_D$ +207.7 (*c* 2.5, $CHCl_3$); IR (neat) 2825, 1739, 1678, 1577, 1372, 1233, 1178, 1038, 790, 755 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.55 (s, 1 H), 6.95 (d, $J$ = 5.0 Hz, 1 H), 6.46 (dd, $J$ = 5.0, 9.5 Hz, 1 H), 6.35 (dd, $J$ = 6.0, 9.5 Hz, 1 H), 5.39 (d, $J$ = 6.0 Hz, 1 H), 3.98 (dd, $J$ = 11.0, 5.0 Hz, 1 H), 3.83 (dd, $J$ = 11.0, 9.0 Hz, 1 H), 3.34 (dd, $J$ = 9.0, 5.0 Hz, 1 H), 2.01 (s, 3 H), 1.99 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 191.8 (CH), 170.8 (C), 169.9 (C), 141.0 (CH), 136.6 (C), 130.1 (CH), 126.7 (CH), 65.2 (CH), 61.5 ($CH_2$), 35.2 (CH), 20.9 ($CH_3$), 20.8 ($CH_3$); MS (*m*/*z*, relative intensity) 238 ($M^+$, 0.8), 178 (4), 165 (11), 136 (10), 107 (42); exact mass calcd for $C_{12}H_{14}O_5$ ($M^+$) 238.0841; found 238.0843.

**Acetic Acid 5-Formyl-6-phenylcyclohexa-2,4-dienyl ester (3h):** $R_f$ 0.60 in 30% EtOAc/hexane; 77% ee; $[\alpha]^{22}_D$ +270.9 (*c* 6.7, $CHCl_3$); IR (neat) 2959, 1735, 1678, 1370, 1238, 1015, 800, 700 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.59 (s, 1 H), 7.26−7.18 (m, 5 H), 7.10−7.08 (m, 1 H), 6.60 (dd, $J$ = 9.5, 5.5 Hz, 1 H), 6.27 (dd, $J$ = 9.5, 5.5 Hz, 1 H), 5.40 (d, $J$ = 5.5 Hz, 1 H), 4.21 (s, 1H), 2.04 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 191.9 (CH), 170.0 (C), 139.7 (CH), 139.5 (C), 139.6 (C), 129.7 (CH), 128.7 (two CH), 127.7 (CH), 127.55 (CH), 127.46 (two CH), 70.0 (CH), 41.2 (CH), 21.1 ($CH_3$); MS (*m*/*z*, relative intensity) 242 ($M^+$, 7), 213 (8), 200 (37), 181 (100), 171 (50), 380 (8), 365 (28); exact mass calcd for $C_{15}H_{14}O_3$ ($M^+$) 242.0943; found 242.0947.

**1-Phenyl-1,5,6,7,8,8a-hexahydronaphthalene-2-carbaldehyde (3i):** $R_f$ 0.6 in 17% EtOAc/hexane; 98% ee; $[\alpha]^{22}_D = -475.9$ (*c* 9.0, $CHCl_3$); IR (neat) 2929, 2854, 1671, 1576, 1200, 699 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 9.43 (s, 1 H), 7.25−7.22 (m, 4 H), 7.18−7.14 (m, 1 H), 6.81 (d, $J$ = 6.0 Hz, 1 H), 5.97 (d, $J$ = 5.5 Hz, 1 H), 3.62 (d, $J$ = 1.5 Hz, 1 H), 2.45 (d, $J$ = 11.5 Hz, 1 H), 2.39−2.37 (m, 1 H), 2.14−2.09 (m, 1 H), 1.99−1.97 (m, 1 H), 1.82−1.77 (m, 2 H), 1.60−1.25 (m, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 192.6 (CH), 157.2 (C), 145.5 (C), 142.5 (CH), 136.5 (C), 128.5 (two CH), 126.9 (two CH), 126.5 (CH), 114.8 (CH), 49.0 (CH), 42.1 (CH), 38.1 ($CH_2$), 36.9 ($CH_2$), 31.7 ($CH_2$), 27.1 ($CH_2$); MS (*m*/*z*, relative intensity) 238 ($M^+$, 70), 209 (84), 167 (80), 115 (28), 91 (100); exact mass calcd for $C_{17}H_{18}O$ ($M^+$) 238.1358; found 238.1351.

**6-Methylcyclohexa-1,3-dienecarbaldehyde (3j):** $R_f$ 0.50 in 5% EtOAc/hexane; 10% ee; $[\alpha]^{22}$ −12.1 (*c* 2.98, $CHCl_3$); IR (neat) 2924, 2854, 1687, 1458, 1377 cm$^{-1}$; $^1$H NMR ($C_6D_6$, 500 MHz) $\delta$ 9.31 (s, 1 H), 6.12−6.08 (m, 1 H), 5.75−5.71 (m, 2 H), 2.81−2.76 (m, 1 H), 2.20−2.00 (m, 1 H), 1.80−1.70 (m, 1 H), 0.85 (d, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR ($C_6D_6$, 125 MHz) $\delta$ 191.90 (CH), 42.74 (C), 140.4 (CH) 134.4 (CH), 123.3 (CH), 30.6 ($CH_2$), 23.2 (CH), 17.8 ($CH_3$); MS (*m*/*z*, relative intensity) 122 ($M^+$, 56), 107 (21), 93 (83), 91 (59), 79 (74), 77 (100); exact mass calcd for $C_8H_{10}O$ ($M^+$) 122.0732; found 122.0730.

**6-Methylcyclohexa-1,3-dienecarboxylic acid (5).** To a solution of **3j** (366 mg, 3.0 mmol) and 2-methyl-2-butene (1 mL, 9.4 mmol) in *t*-BuOH (7.5 mL) was added a freshly prepared solution of sodium chlorite (140 mg, 1.55 mmol) in 20% w/w aqueous $NaH_2PO_4$ (2.4 g in 12 mL of $H_2O$) at room temperature, and the resulting solution was stirred for 8 h. The mixture was diluted with ethyl acetate (30 mL) and washed with water (4 mL). The aqueous phase was extracted with ethyl acetate (30 mL), and the combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc/hexane ($R_f$ = 0.50 in 30% EtOAc/hexane) to give acid **5** as a colorless oil (315 mg, 76% yield): 10% ee; $[\alpha]^{20}_D = -10.2$ (*c* 4.3, $CHCl_3$); IR (neat) 3400−3000, 2962, 1680, 1572, 1421, 1273, 700 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 7.08 (d, $J$ = 3.5 Hz, 1 H), 6.07−6.01 (m, 2 H), 2.80−2.72 (m, 1 H), 2.58−2.44 (m, 1 H), 2.22−2.16 (m, 1 H), 0.97 (d, $J$ = 6.5 Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 172.7 (C), 134.1 (CH), 132.8 (CH), 131.6 (C), 123.0 (CH), 30.7 ($CH_2$), 24.9 (CH), 17.6 ($CH_3$); MS (*m*/*z*, relative intensity) 138 ($M^+$, 30),123 (10), 105 (9), 93 (100), 91 (36), 79 (45), 77 (67); exact mass calcd for $C_8H_{10}O_2$ ($M^+$) 138.0681; found 138.0681.

**6-Methylcyclohexa-1,3-dienecarboxylic acid methyl ester (6).** To a solution of **5** (276 mg, 2.0 mmol) in $CH_2Cl_2$ (5 mL) was added a solution of $CH_2N_2-Et_2O$. The solution was stirred for 30 min and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f = 0.30$ in 3% EtOAc/hexane) to give ester **6** as a colorless oil (273 mg, 75% yield): 7% ee; $[\alpha]^{22}_D = -6.7$ (*c* 1.32, $CHCl_3$);[53] IR (neat) 2926, 1712, 1444, 1257, 1022, 771 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 6.93 (s, 1 H), 6.05−5.95 (m, 2 H), 3.73 (s, 3 H), 2.80−2.72 (m, 1 H), 2.60−2.40 (m, 1 H), 2.15 (d, $J = 17.0$ Hz, 1 H), 0.96 (d, $J = 7.0$ Hz, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 167.7 (C), 132.3 (C), 131.9 (CH), 131.5 (CH), 123.0 (CH), 51.5 ($CH_3$), 30.6 ($CH_2$), 25.3 (CH), 17.7 ($CH_3$);[54] MS (*m*/*z*, relative intensity) 152 ($M^+$, 20), 137 (8), 121 (16), 105 (8), 93 (100); exact mass calcd for $C_9H_{12}O_2$ ($M^+$) 152.0837; found 152.0835.

**4-Methyl-6-phenylcyclohexa-1,3-dienecarboxylic acid (7).** To a solution of **3d** (47.5 mg, 0.24 mmol, 56% ee) and 2-methyl-2-butene (3 mL) in *t*-BuOH (12 mL) was added a freshly prepared solution of sodium chlorite (140 mg, 1.55 mmol) in 20% w/w aqueous $NaH_2PO_4$ (2.4 g in 12 mL of $H_2O$) at room temperature, and the resulting solution was stirred for 5 h. The mixture was diluted with ethyl acetate (30 mL) and washed with water (4 mL). The aqueous phase was extracted with ethyl acetate (30 mL), and the combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc/hexane ($R_f = 0.3$ in 20% EtOAc/hexane) to give acid **7** as a white solid (41 mg, 80% yield): mp 138−140 °C; $[\alpha]^{25}_D = -146.6$ (*c* 1.5, MeOH); mp 138−140 °C; IR (neat) 3600, 2922, 1668, 1576, 1417, 1288, 1238, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.35−7.10 (m, 6 H), 5.90 (br s, 1 H), 3.93 (d, $J = 10.5$ Hz, 1 H), 2.90−2.80 (m, 1 H), 2.34 (d, $J = 17.5$ Hz, 1 H), 1.77 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 171.9 (C), 144.1 (C), 143.2 (C), 137.0 (CH), 128.4 (two CH), 127.0 (two CH), 126.5 (CH), 125.8 (C), 119.1 (CH), 37.6 ($CH_2$), 36.3 (CH), 23.9 ($CH_3$); MS (*m*/*z*, relative intensity) 214 ($M^+$, 82), 181 (36), 169 (100), 154 (22); exact mass calcd for $C_{14}H_{14}O_2$ ($M^+$) 214.0994; found 214.0994.

**4-Methyl-6-phenylcyclohexa-1,3-dienecarboxylic acid ethyl ester (8).** A solution of **7** (21 mg, 0.1 mmol), benzene (0.35 mL), and concd $H_2SO_4$ (0.1 mL) in ethanol (5 mL) was heated to reflux for 24 h. The solution was cooled to room temperature, saturated aqueous $NaHCO_3$ solution (10 mL) was added and stirred for 10 min. The solution was diluted with EtOAc (15 mL × 2) and washed with brine. The combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 5% EtOAc/hexane ($R_f = 0.3$ in 5% EtOAc/hexane) to give ester **8** as a yellow oil (20 mg, 85% yield): $R_f$ 0.30 in 5% EtOAc.hexane; 56% ee; $[\alpha]^{22}_D = -90.7$ (*c* 13, $C_6H_6$);[55] IR (neat) 2927, 1705, 1589, 1267, 1076, 760, 698 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 7.25−7.10 (m, 6 H), 5.89 (br s, 1 H), 4.14−4.06 (m, 2 H), 3.98 (d, $J = 10.5$ Hz, 1 H), 2.90−2.83 (m, 1 H), 2.34 (d, $J = 17.5$ Hz, 1 H), 1.77 (s, 3 H), 1.19 (t, $J = 7.0$ Hz, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 167.4 (C), 144.0 (C), 142.8 (C), 134.8(CH), 128.6 (two CH), 127.33 (two CH), 127.26 (C), 126.7 (CH), 119.2 (CH), 60.4 ($CH_2$), 37.7 ($CH_2$), 37.1 (CH), 24.0 ($CH_3$), 14.4 ($CH_3$);[54] MS (*m*/*z*, relative intensity) 242 ($M^+$, 100), 227 (22), 169 (84), 154 (36), 91 (66), 77 (79); exact mass calcd for $C_{16}H_{18}O_2$ ($M^+$) 242.1307; found 242.1309.

**Acetic Acid 2-Acetoxymethyl-3-formyl-5,6-dihydroxycyclohex-3-enyl ester (9).** To a solution of **3g** (286 mg, 1.2 mmol) in THF/*t*-BuOH−$H_2O$ (10:30:5 mL) was added *N*-methylmorpholine *N*-oxide (NMO, 351 mg, 3 mmol), and the solution was stirred for 10 min at ambient temperature. $OsO_4$ (0.1 mL, 2.5 wt % in *t*-BuOH) was added, and stirring was maintained at ambient temperature for ca. 36 h. The reaction was quenched by the addition of sodium hydrosulfite (0.2 g), Florisil (2.0 g), and $H_2O$ (5 mL). The mixture was stirred for 30 min, washed with acetone (30 mL), filtered through filter paper, and extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine (15 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 85% EtOAc/hexane ($R_f$ 0.28 in 80% EtOAc/hexane) to give **9** (212 mg; 65% yield) as a pale yellow oil: $[\alpha]^{22}_D = -28.1$ (*c* 13.3, $CHCl_3$); IR (neat) 3550−3100, 2920, 1735, 1686, 1375, 1247, 1039 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 9.48 (s, 1 H), 6.79 (br s, 1 H), 5.32 (dd, $J = 5.5$, 4.0 Hz, 1 H), 4.55−4.50 (m, 2 H), 4.20 (dd, $J = 5.5$, 4.0 Hz, 1 H), 3.98 (br s, 1 H), 3.29 (br s, 1 H), 2.97 (br s, 1 H), 2.90 (br s, 1 H), 2.06 (s, 6 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 192.8 (CH), 171.5 (C), 170.6 (C), 149.4 (CH), 138.4 (C), 69.9 (CH), 68.6 (CH), 66.0 (CH), 62.2 ($CH_2$), 37.9 (CH), 21.0 ($CH_3$), 20.9 ($CH_3$); MS (*m*/*z*, relative intensity) 272 ($M^+$, 16), 229 (26), 133 (20), 119 (46), 57 (100); exact mass calcd for $C_{12}H_{16}O_7$ ($M^+$) 272.0896; found 272.0893.

**Acetic Acid 5-Acetoxymethyl-6-formyl-2,2-dimethyl-3a,4,5,-7a-tetrahydrobenzo[1,3]dioxol-4-yl ester (10).** To a solution of **9** (100 mg, 0.36 mmol) in dry acetone (7 mL) was added 2,2-dimethoxypropane (114 mg, 1.1 mmol). The resulting solution was stirred for 5 min at ambient temperature, *p*-TsOH (28 mg, 0.15 mmol) was added, and stirring was maintained at ambient temperature for 12 h. The reaction was quenched with aq $NaHCO_3$ (15 mL), extracted with EtOAc (30 mL × 2), washed with brine (30 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The crude residue was purified by flash column chromatography with 40% EtOAc/hexane ($R_f$ 0.83 in 80% EtOAc/hexane) to give **10** (96 mg, 85% yield) as a colorless oil: $[\alpha]^{22}_D = +15.1$ (*c* 13, $CHCl_3$); IR (neat) 2921, 2850, 1743, 1697, 1458, 1225, 741 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 9.54 (s, 1 H), 6.77 (d, $J = 3.5$ Hz, 1 H), 5.61 (s, 1 H), 4.83 (dd, $J = 3.5$, 4.0 Hz, 1 H), 4.39 (br s, 1 H), 4.24−4.20 (m, 2 H), 3.09 (dd, $J = 7.0$ Hz, 1 H), 2.09 (s, 3 H), 2.05 (s, 3 H), 1.43 (s, 3 H), 1.41 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 192.9 (CH), 170.7 (C), 169.5 (C), 146.0 (CH), 138.0 (C), 110.6 (C), 73.3 (CH), 70.7 (CH), 67.7 (CH), 62.4 ($CH_2$), 35.8 (CH), 27.5 ($CH_3$), 25.6 ($CH_3$), 20.93 ($CH_3$), 20.88 ($CH_3$); MS (*m*/*z*, relative intensity) 297 ($M^+$ − Me, 54), 297 (54), 177 (19), 165 (32), 135 (100); exact mass calcd for $C_{15}H_{20}O_7$ ($M^+$) 312.1209; found 312.1211.

**Acetic Acid 4-Acetoxy-6-formyl-2,2-dimethylhexahydrobenzo-[1,3]dioxol-5-ylmethyl ester (11 and 12).** A suspension of **10** (235 mg, 1.5 mmol) and Pd−C (20 mg, 10%) in EtOAc (30 mL) was stirred at room temperature under hydrogen (1 atm) for 6 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give the crude product. The two isomers of the product **12** to **11** were shown to be 1:7, analyzed by $^1H$ NMR analysis. The residue was purified by flash column chromatography with 45% EtOAc/hexane (**12**: $R_f = 0.51$; **11**: $R_f = 0.39$ in 50% EtOAc/hexane) to give **12** and **11** as the colorless oils. Indeed, isomerization of **11** to **12** was occurred gradually at ambient temperature and that can be accelerated by the addition of $Et_3N$ and silica gel. In practice, the crude residue was purified by silica gel column chromatography with 1:45:54 $Et_3N$/EtOAc/hexane (**12**: $R_f = 0.51$; **11**: $R_f = 0.39$ in 50% EtOAc/hexane) over 2 h to give **12** (153 mg, 65%) as a colorless oil: $[\alpha]^{22}_D = -17.5$ (*c* 6.9, $CH_3OH$); IR (neat) 2925, 1742, 1372, 1225, 1051 $cm^{-1}$; $^1H$ NMR ($C_6D_6$, 500 MHz) $\delta$ 9.20 (s, 1 H), 5.36−5.25 (m, 1 H), 4.20−4.14 (m, 1 H), 4.04−4.00 (m, 1 H), 3.95−3.90 (m, 1 H), 3.80−3.70 (m, 1 H), 1.95−1.85 (m, 1 H), 1.82−1.75 (m, 1 H), 1.71 (s, 3 H), 1.65 (s, 3 H), 1.52 (s, 3 H), 1.40−1.20 (m, 2 H), 1.16 (s, 3 H); $^{13}C$ NMR ($C_6D_6$, 125 MHz) $\delta$ 200.5 (CH), 170.0 (C), 169.3 (C), 109.2 (C),

(53) For $[\alpha]^{23}_D = +95.8$ (*c* 1.17, $CHCl_3$) for 100% ee of the *R* enantiomer, see: Davies, S. G.; Bhalay, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1595.

(54) Moorhoff, C. M. *Synlett* **1997**, 126.

(55) (a) For $[\alpha]^{20}_D = -14.5$ (*c* 1.0, $C_6H_6$) for 7.8% ee of the *R*-enantiomer, see: Serebryakov, E. P.; Nigmatov, A. G.; Shcherbakov, M. A.; Struchkova, M. I. *Russ. Chem. Bull. Int. Ed.* **1998**, *47*, 82. (b) For $[\alpha]^{20}_D = -52$ (*c* 1.0, $C_6H_6$) for 28% ee of the *R*-enantiomer, see: Nigmatov, A. G.; Serebryakov, E. P. *Russ. Chem. Bull. Int. Ed.* **1996**, *45*, 623.

76.9 (CH), 72.4 (CH), 70.6 (CH), 62.2 ($CH_2$), 45.0 (CH), 38.2 (CH), 27.4 ($CH_3$), 25.8 ($CH_2$), 25.5 ($CH_3$), 20.4 ($CH_3$), 20.3 ($CH_3$); MS (*m*/*z*, relative intensity) 315 ($M^+ + 1$, 45), 256 (38), 213 (41), 171 (32), 153 (100); exact mass calcd for $C_{15}H_{22}O_7$ ($M^+$) 314.1366; found 314.1371. For **11**: $[\alpha]^{22}_D = -27.8$ (*c* 11.5, $CH_3OH$); IR (neat) 2925, 2853, 1742, 1372, 1225, 1051 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 9.77 (s, 1 H), 5.50−5.42 (m, 1 H), 4.41−4.30 (m, 2 H), 4.25−4.20 (m, 1 H), 4.03−4.00 (m, 1 H), 2.78 (br s, 1 H), 2.45−2.40 (m, 1 H), 2.20−2.00 (m, 2 H), 2.12 (s, 3 H), 2.03 (s, 3 H), 1.48 (s, 3 H), 1.34 (s, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 200.9 (CH), 170.5 (C), 170.0 (C), 109.9 (C), 77.9 (CH), 73.3 (CH), 70.9 (CH), 62.5 ($CH_2$), 45.9 (CH), 39.6 (CH), 27.5 ($CH_3$), 26.43 ($CH_2$), 26.38 ($CH_3$), 21.0 ($CH_3$), 20.8 ($CH_3$); MS (*m*/*z*, relative intensity) 315 ($M^+ + 1$, 5), 299 (100), 287 (13), 197 (30), 137 (71); exact mass calcd for $C_{15}H_{22}O_7$ ($M^+$) 314.1366; found 314.1371.

**Acetic Acid 5-Acetoxymethyl-6-hepta-1,3-dienyl-2,2-dimethylhexahydrobenzo[1,3]dioxol-4-yl ester (13).** To a solution of (2*E*)-hexenyltriphenylphosphonium bromide (74 mg, 0.17 mmol) in THF (15 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.1 mL, 0.17 mmol) at −78 °C. The solution was stirred at −78 °C for 30 min, followed by the addition of a solution of **12** (41 mg, 0.13 mmol) in THF (5 mL) and was warmed up to room temperature over 2 h. The reaction was quenched by the addition of saturated aqueous $NH_4Cl$ (10 mL). The solution was extracted with EtOAc (20 mL × 2). The combined organic layers were washed with brine (10 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography with 20% EtOAc/hexane ($R_f$ 0.83 in 50% EtOAc/*n*-hexane) to give the mixture of **13** and (*Z*)-**13** (42 mg; 85% yield) as a pale yellow oil, in a ratio of 3:1. The isomers were separated by HPLC (Rainin Solvent Delivery System Dynamax SD-200, detector: Dynamax UV-C, Spherisorb Phase Sep S10 W, 25 cm × 10 cm, semi-prep column, 25 cm × 10 mm, rate: 5 mL/min; for **13**, $R_t$ 18.19; for (*Z*)-**13**, $R_t$ 20.11). For **13**: $[\alpha]^{22}_D = -51.0$ (*c* 14, $CHCl_3$); IR (neat) 2925, 2856, 1745, 1462, 1377, 1240, 1049 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 6.06 (dd, *J* = 10.5, 15.0 Hz, 1H), 5.95 (dd, *J* = 14.0, 10.5 Hz, 1 H), 5.68−5.55 (m, 1 H), 5.27 (dd, *J* = 15.0, 9.5 Hz, 1 H), 5.13 (dd, *J* = 10.0, 8.5 Hz, 1 H), 4.30 (br s, 1 H), 4.18 (d, *J* = 11.5 Hz, 1 H), 3.99−3.96 (m, 1 H), 3.81 (d, *J* = 11.5 Hz, 1 H), 2.58−2.41 (m, 1 H), 2.13 (d, *J* = 15.5 Hz, 1 H), 2.04 (s, 3 H), 2.00 (s, 3 H), 2.04−2.00 (m, 2 H), 1.63−1.56 (m, 1 H), 1.55 (s, 3 H), 1.49 (dd, *J* = 10.0, 11.0 Hz, 1 H), 1.41−1.36 (m, 2 H), 1.34 (s, 3 H), 0.88 (t, *J* = 7.5 Hz, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 171.0 (C), 170.0 (C), 134.4 (CH), 132.4 (CH), 131.5 (CH), 129.7 (CH), 109.2 (C), 78.2 (CH), 73.6 (CH), 72.3 (CH), 61.2 ($CH_2$), 43.2 (CH), 36.0 (CH), 34.7 ($CH_2$), 33.0 ($CH_2$), 27.7 ($CH_3$), 26.1 ($CH_3$), 22.4 ($CH_2$), 21.0 ($CH_3$), 20.8 ($CH_3$), 13.7 ($CH_3$); MS (*m*/*z*, relative intensity) 380 ($M^+$, 1), 365 (28), 320 (27), 260 (19), 244 (20), 219 (18), 202 (100), 173 (79), 159 (55); exact mass calcd for $C_{21}H_{32}O_6$ ($M^+$) 380.2199; found 380.2200.

**Acetic Acid 4-Acetoxy-6-hepta-1,3-dienyl-2,2-dimethylhexahydrobenzo[1,3]dioxol-5-ylmethyl ester ((*Z*)-13):** $[\alpha]^{22}_D = -7.2$ (*c* 15.3, $CHCl_3$); IR (neat) 2985, 2959, 2931, 2873, 1744, 1382, 1239, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 6.28 (dd, *J* = 14.0, 11.5 Hz, 1H), 6.02 (dd, *J* = 11.0, 10.5 Hz, 1 H), 5.70−5.60 (m, 1 H), 5.19 (dd, *J* = 10.5, 8.0 Hz, 1 H), 4.92 (dd, *J* = 10.5, 10.0 Hz, 1 H), 4.32 (br s, 1 H), 4.11 (d, *J* = 11.0 Hz, 1 H), 3.97 (dd, *J* = 7.5, 5.5 Hz, 1 H), 3.80 (dd, *J* = 11.5, 3.0 Hz, 1 H), 2.20−1.90 (m, 3 H), 2.04 (s, 3 H), 1.98 (s, 3 H), 1.65−1.52 (m, 1 H), 1.60 (s, 3 H), 1.50−1.30 (m, 4 H), 1.35 (s, 3 H), 0.88 (t, *J* = 7.5 Hz, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 170.7 (C), 169.8 (C), 136.3 (CH), 130.8 (CH), 129.0 (CH), 125.2 (CH), 109.0 (C), 78.2 (CH), 73.5 (CH), 72.0 (CH), 60.7 ($CH_2$), 43.0 (CH), 37.8 ($CH_2$), 32.6 ($CH_2$), 30.9 (CH), 27.6 ($CH_3$), 26.0 ($CH_3$), 22.3 ($CH_2$), 20.8 ($CH_3$), 20.6 ($CH_3$), 13.5 ($CH_3$); MS (*m*/*z*, relative intensity) 381 ($M^+ + 1$, 2) 365 (47), 320 (58), 202 (60), 173 (48), 43 (100); exact mass calcd for $C_{21}H_{32}O_6$ ($M^+$) 380.2199; found 380.2200.

**6-Hepta-1,3-dienyl-5-hydroxymethyl-2,2-dimethylhexahydrobenzo[1,3]dioxol-4-ol (14).** To a solution of **13** (75 mg, 0.19 mmol) in $CH_3OH$ (15 mL) was added $K_2CO_3$ (22 mg, 0.16 mmol) at room temperature. The solution was stirred for 3 h at ambient temperature until the reaction completed, monitored by TLC. The reaction was quenched by the addition of $H_2O$ (8 mL); the solution was extracted with EtOAc (20 mL × 2), dried over $Na_2SO_4$, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 3% EtOAc/hexane ($R_f$ = 0.25 in 50% EtOAc/hexane) to give **14** as a colorless oil (104 mg, 90% yield): mp 104−105 °C; $[\alpha]^{22}_D = -52.8$ (*c* 4.6, $CHCl_3$); IR (neat) 3600−3200, 2927, 2862, 1728, 1668, 1460, 1379, 1244, 1221, 1070, 989 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 6.05−5.92 (m, 2 H), 5.62−5.55 (m, 1 H), 5.28 (dd, *J* = 14.5, 9.5 Hz, 1 H), 4.27 (br s, 1 H), 3.90−3.80 (m, 2 H), 3.69 (dd, *J* = 10.0, 8.5 Hz, 1 H), 3.58 (dd, *J* = 7.5, 7.0 Hz, 1 H), 3.43 (br s, 1 OH), 2.93 (br s, 1 OH), 2.25−2.15 (m, 1 H), 2.10−1.95 (m, 3 H), 1.63−1.55 (m, 1 H), 1.50 (s, 3 H), 1.42−1.30 (m, 3 H), 1.34 (s, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 134.1 (CH), 132.5 (CH), 131.9 (CH), 129.7 (CH), 108.9 (C), 81.2 (CH), 76.3 (CH), 73.6 (CH), 64.1 ($CH_2$), 45.9 (CH), 36.4 (CH), 34.6 ($CH_2$), 33.4 ($CH_2$), 28.4 ($CH_3$), 26.2 ($CH_3$), 22.4 ($CH_2$), 13.7 ($CH_3$); MS (*m*/*z*, relative intensity) 296 ($M^+$, 1), 247 (10), 231 (34), 230 (20), 215 (14), 181 (12), 131 (19), 117 (100), 69 (33); exact mass calcd for $C_{17}H_{28}O_4$ ($M^+$) 296.1988; found 296.1988.

**5-(*tert*-Butyldimethylsilanyloxymethyl)-6-hepta-1,3-dienyl-2,2-dimethylhexahydrobenzo[1,3]dioxol-4-ol (15).** To a solution of **14** (20 mg, 0.07 mmol), imidazole (5 mg, 0.08 mmol), and 4-dimethylaminopyridine (1 mg, 0.01 mmol) in $CH_2Cl_2$ (10 mL) was added *tert*-butyldimethylsilyl chloride (13 mg, 0.08 mmol) at room temperature. The solution was stirred for 2 h at room temperature. The reaction was quenched by the addition of $H_2O$ (5 mL); the solution was extracted with EtOAc (15 mL × 2), dried over $Na_2SO_4$, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc/hexane ($R_f$ = 0.26 in 20% EtOAc/hexane) to give acetate **15** as a colorless oil (26 mg, 92% yield): $[\alpha]^{22}_D = -37.2$ (*c* 7.7, $CHCl_3$); IR (neat) 3465, 2962, 2929, 2862, 1466, 1379, 1246, 1092, 839, 775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 5.90−6.05 (m, 2 H), 5.52−5.60 (m, 1 H), 5.20−5.30 (m, 1 H), 4.26 (br s, 1 H), 3.82−3.88 (m, 1 H), 3.75 (dd, *J* = 10.0, 8.5 Hz, 1H), 3.53 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.48 (br s, 1 OH), 2.20−2.30 (m, 1 H), 1.20−1.30 (m, 1 H), 1.34 (s, 3 H), 1.30−1.40 (m, 2 H), 1.50 (s, 3 H), 1.55−1.65 (m, 1 H), 1.95−2.08 (m, 3 H), 0.86 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.01 (s, 6 H); $^{13}C$ NMR ($CDCl_3$, 125 MHz) $\delta$ 133.7 (CH), 132.5 (CH), 131.9 (CH), 129.8 (CH), 108.7 (C), 81.3 (CH), 74.8 (CH), 73.5 (CH), 63.5 ($CH_2$), 45.9 (CH), 35.6 (CH), 34.7 ($CH_2$), 33.2 ($CH_2$), 28.4 ($CH_3$), 26.3 ($CH_3$), 25.8 (three $CH_3$), 22.4 ($CH_2$), 18.1 (C), 13.7 ($CH_3$), −5.7 (two $CH_3$); MS (*m*/*z*, relative intensity) 410 ($M^+$, 2), 395 (11), 353 (11), 295 (50), 277 (82), 189 (40), 75 (100); exact mass calcd for $C_{23}H_{42}O_4Si$ ($M^+$) 410.2852; found 410.2850.

**5-(*tert*-Butyldimethylsilanyloxymethyl)-6-hepta-1,3-dienyl-2,2-dimethyltetrahydrobenzo[1,3]dioxol-4-one (16).** To a solution of **15** (26 mg, 0.06 mmol) in $CH_2Cl_2$ (10 mL) was added Dess−Martin periodinane (31 mg, 0.07 mmol) at room temperature, and the resulting solution was stirred for 1 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL). The mixture was extracted with ethyl acetate (10 mL × 2), washed with water (5 mL), and the combined organic layers were dried over $Na_2SO_4$ and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 20% EtOAc/hexane ($R_f$ = 0.56 in 20% EtOAc/hexane) to give **16** as a yellow oil (22 mg, 90% yield): $[\alpha]^{22}_D = -17.9$ (*c* 3.8, $CHCl_3$); IR (neat) 2931, 2852, 1728, 1464, 1379, 1254, 1103, 837, 777 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 500 MHz) $\delta$ 6.08−5.93 (m, 2 H), 5.63−5.56 (m, 1 H), 5.39 (dd, *J* = 9.5, 15.5 Hz, 1 H), 4.53 (br s, 1 H), 4.25 (d, *J* = 5.0 Hz, 1 H), 3.79 (br s, 2 H), 2.75−2.65 (m, 1 H), 2.22−2.17 (m, 2 H), 2.05−1.92 (m, 2 H), 1.90 (dd, *J* = 14.0, 12.5 Hz, 1 H), 1.42−

1.30 (m, 2 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 0.88 (t, $J$ = 7.0 Hz, 3 H), 0.83 (s, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 206.5 (C), 134.4 (CH), 131.8 (CH), 131.5 (CH), 129.7 (CH), 109.8 (C), 79.0 (CH), 76.0 (CH), 58.7 ($CH_2$), 55.8 (CH), 38.2 (CH), 34.7 ($CH_2$), 33.1 ($CH_2$), 27.0 ($CH_3$), 26.0 ($CH_3$), 25.8 (three $CH_3$), 22.4 ($CH_2$), 18.2 (C), 13.7 ($CH_3$), −5.57 ($CH_3$), −5.63 ($CH_3$); MS (*m*/*z*, relative intensity) 408 ($M^+$, 2), 393 (12), 351 (100), 293 (62), 263 (75), 171 (76), 75 (55); exact mass calcd for $C_{23}H_{40}O_4Si$ ($M^+$) 408.2696; found 408.2697.

**6-Hepta-1,3-dienyl-5-hydroxymethyl-2,2-dimethyltetrahydrobenzo[1,3]dioxol-4-one (17).** To a solution of **16** (22 mg, 0.05 mmol) in $CH_3CN$ (8 mL) was added HF/pyridine (5 mg, 0.05 mmol) at 25 °C, and the resulting solution was stirred for 2 h. The reaction was quenched by the addition of silica gel (5 mg), and the resulting mixture was passed through a small silica gel column; 50% EtOAc/hexane was used as eluent for the flash column chromatography separation to give **17** as a white solid (4 mg, 88% yield): $[\alpha]^{23}_D$ = −39.8 (*c* 1.5, $CHCl_3$); lit. $[\alpha]^{25}_D$ = +34.8 (*c* 0.95, $CHCl_3$) for (+)-**17**.[56] IR (neat) 3600−3300, 2953, 2925, 1726, 1460, 1380, 1273, 1123, 1074, 990 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.09 (dd, $J$ = 15.0, 10.5 Hz, 1 H), 5.99 (dd, $J$ = 15.0, 10.5 Hz, 1 H), 5.64 (dt, $J$ = 15.0, 7.5 Hz, 1 H), 5.33 (dd, $J$ = 15.0, 9.0 Hz, 1 H), 4.55 (br s, 1 H), 4.30 (d, $J$ = 5.5 Hz, 1 H), 3.73 (br s, 2 H), 2.70−2.60 (m, 1 H), 2.44 (t, $J$ = 7.0 Hz, 1 H), 2.45−2.40 (m, 1 H), 2.36−2.32 (m, 1 H), 2.03 (q, $J$ = 7.5 Hz, 2 H), 1.97−1.90 (m, 1 H), 1.42 (s, 3 H), 1.40−1.30 (m, 2 H), 1.37 (s, 3 H), 0.88 (t, $J$ = 7.5 Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 210.3 (C), 135.3 (CH), 132.7 (CH), 130.2 (CH), 129.3 (CH), 109.9 (C), 79.1 (CH), 76.3 (CH), 59.9 ($CH_2$), 54.9 (CH), 38.6 (CH), 34.7 ($CH_2$), 33.0 ($CH_2$), 27.0 ($CH_3$), 26.0 ($CH_3$), 22.3 ($CH_2$), 13.7 ($CH_3$);[56] MS (*m*/*z*, relative intensity) 294 ($M^+$, 11), 263 (70), 205 (20), 43 (100); exact mass calcd for $C_{17}H_{26}O_4$ ($M^+$) 294.1831; found 294.1829.

**3-Hepta-1,3-dienyl-5,6-dihydroxy-2-hydroxymethylcyclohexanone (18).** To a solution of **17** (12 mg, 0.041 mmol) in MeOH (3 mL) was added a solution of methanolic HCl (0.1 mL, prepared from 0.05 mL concd HCl in 2 mL of MeOH). The resulting mixture was stirred for 3 h at ambient temperature until the reaction was completed, monitor by TLC. The reaction was quenched by the addition of aqueous saturated $NaHCO_3$ solution (2 mL). The solution was diluted with EtOAc (10 mL), washed with brine (2 mL), dried over $Na_2SO_4$, and concentrated in vacuo to give the crude product. The residue was purified by flash column chromatography with 50% EtOAc/hexane ($R_f$ = 0.63 in 75% EtOAc/hexane) to give **18** as white solid (10 mg, 95% yield): $[\alpha]^{22}_D$ = +4.3 (*c* 2.3, $CHCl_3$); lit. $[\alpha]^{23}_D$ = +4.49 (*c* 0.32, $CHCl_3$);[57] $[\alpha]_D^{23}$ +4.4 (C 0.8, $CHCl_3$);[58] IR (neat) 3550−3100, 2923, 2851, 1718, 1670, 1460, 1108, 989 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$ 6.09 (dd, $J$ = 15.0, 10.5 Hz, 1H), 5.97 (dd, $J$ = 15.0, 10.0 Hz, 1H), 5.66−5.60 (m, 1H), 5.37 (dd, $J$ = 15.0, 9.5 Hz, 1H), 4.35 (br s, 1 H), 4.19 (br s, 1H), 3.82 (br s, 1 OH), 3.77 (br s, 2 H), 2.84−2.78 (m, 1 H), 2.52 (br s, 1 OH), 2.41−2.35 (m, 1 H), 2.32 (br s, 1 OH), 2.18−2.10 (m, 1 H), 2.00−2.08 (m, 2 H), 1.84 (dd, $J$ = 13.5, 13.5 Hz, 1 H), 1.40−1.32 (q, $J$ = 7.5 Hz, 2 H), 0.88 (t, $J$ = 7.5 Hz, 3 H); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$ 211.5 (C), 135.2 (CH), 132.8 (CH), 131.0 (CH), 129.3 (CH), 77.1 (CH), 71.7 (CH), 59.7 ($CH_2$), 54.6 (CH), 39.1 (CH), 35.3 ($CH_2$), 34.7 ($CH_2$), 22.4 ($CH_2$), 13.7 (CH);[57,59] MS (*m*/*z*, relative intensity) 254 ($M^+$, 7), 236 (11), 223 (100), 205 (39), 149 (79); exact mass calcd for $C_{14}H_{22}O_4$ ($M^+$) 254.1518; found 254.1518.

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**Supporting Information Available:** Spectra data for the new compounds (**3a**−**18**) and X-ray crystallographic data for compound **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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