Total Synthesis of (−)-Solanapyrone A via Enzymatic Diels−Alder Reaction of Prosolanapyrone

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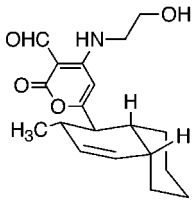
The syntheses of prosolanapyrones I (**6**) and II (**7**) via the aldol reactions of pyrone and dienal segments have been achieved in five steps in 31% overall yield for **6** and seven steps in 5% overall yield for **7**. An improved synthetic route starting from vinylpyrone **27** provided **7** in 11 steps in 12% overall yield. The enzymatic Diels−Alder reaction of **7** affords (−)-solanapyrone A (**1**) with high enantioselectivity and with good exo-selectivity, which is difficult to attain by chemical methods. In addition, a crude enzyme preparation from *Alternaria solani* has been used to perform a kinetic resolution of (±)-**3**.

Introduction

Solanapyrones were isolated as phytotoxic substances from phytopathogenic fungi *Alternaria solani*[1−3] and *Ascochyta rabiei*.[4] The solanapyrone family consists of diastereomers A (**1**) and D (**2**) and their reduced forms B (**3**), E (**4**),[5] and C (**5**) that possess alternate side chains at C-13. Isolation of these substances as optically active

1 R = CHO
3 R = CH_2OH

2 R = CHO
4 R = CH_2OH



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forms strongly suggest that solanapyrones are biosynthesized from the achiral linear triene precursor prosolanapyrone III (**8**) via an enzyme-catalyzed Diels−Alder reaction.[3,6] Incorporation of an isotopically labeled biosynthetic precursor, prosolanapyrone II (**7**) into (−)-solanapyrones unambiguously confirmed the biosynthetic pathway of solanapyrones as shown in Scheme 1.[5] In a subsequent study, we found enzymatic activity catalyzing the Diels−Alder reaction in cell-free extracts of *A. solani*,[7] and we reported the partial purification and properties of the enzyme, solanapyrone synthase,[8] which is the first example of a "Diels−Alderase". In addition, we showed that in the presence of molecular oxygen the crude enzyme converted **7** to **1** and **2** with accompanying formation of hydrogen peroxide. Current evidence suggests that the single enzyme catalyzes oxidation and Diels−Alder reactions in a two-step conversion, although the enzyme was not purified as a single band on SDS−PAGE.[8]

Enzymes are now firmly established as useful tools for syntheses of organic molecules with their capability for performing asymmetric transformation under mild conditions.[9,10] In organic synthesis, however, use of enzymes for carbon−carbon bond formation is limited to aldolases, prenyl diphosphate synthase, and a few other examples.[9,10] In this paper, we illustrate the application of a Diels−Alderase in the context of an efficient asymmetric synthesis of (−)-solanapyrone A (**1**) with good exo-selectivity, which is difficult to achieve by chemical methods.

Synthesis of Prosolanapyrones via Aldol Condensations of Pyrones and Dienal. Total synthesis of (±)-**1** was completed by intramolecular Diels−Alder reaction of a triene intermediate which was prepared by the aldol reaction of a pyrone segment with a dienal segment.[11] Although this convergent route was straightforward and short, a major drawback was the capricious yield of the aldol condensation. We essentially adopted this biomimetic route and made an effort to improve the

(1) Ichihara, A.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett.* **1983**, *24*, 5373−5376.
(2) Ichihara, A.; Miki, M.; Sakamura, S. *Tetrahedron Lett.* **1985**, *26*, 2453−2454.
(3) Oikawa, H.; Yokota, T.; Ichihara, A.; Sakamura, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1284−1285.
(4) Alam, S. S.; Bilton, J. M.; Slawin, M. Z.; Williams, D. J.; Sheppard, R. N.; Strange, R. M. *Phytochemistry* **1989**, *28*, 2627−2630.
(5) Oikawa, H.; Suzuki, Y.; Naya, A.; Katayama, K.; Ichihara, A. *J. Am. Chem. Soc.* **1994**, *116*, 3605−3606.
(6) Oikawa, H.; Yokota, T.; Abe, T.; Ichihara, A.; Sakamura, S.; Yoshizawa, Y.; Vederas, J. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1282−1284.
(7) Oikawa, H.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1321−1322. Ichihara, A.; Oikawa, H. *Dynamic Aspects of Natural Products Chemistry: Molecular Biological Approaches*; Ogura, K., Sankawa, U., Eds.; Koudannsha Scientific: Tokyo, 1997; pp 119−144.
(8) Katayama, K.; Kobayashi, T.; Oikawa, H.; Honma, M.; Ichihara, A. *Biochim. Biophys. Acta* **1998**, *1384*, 387−395.
(9) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis*; VCH Publishers: New York, 1995.
(10) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev.* **1992**, *92*, 1071−1140.
(11) Ichihara, A.; Miki, M.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett.* **1987**, *28*, 1175−1178.

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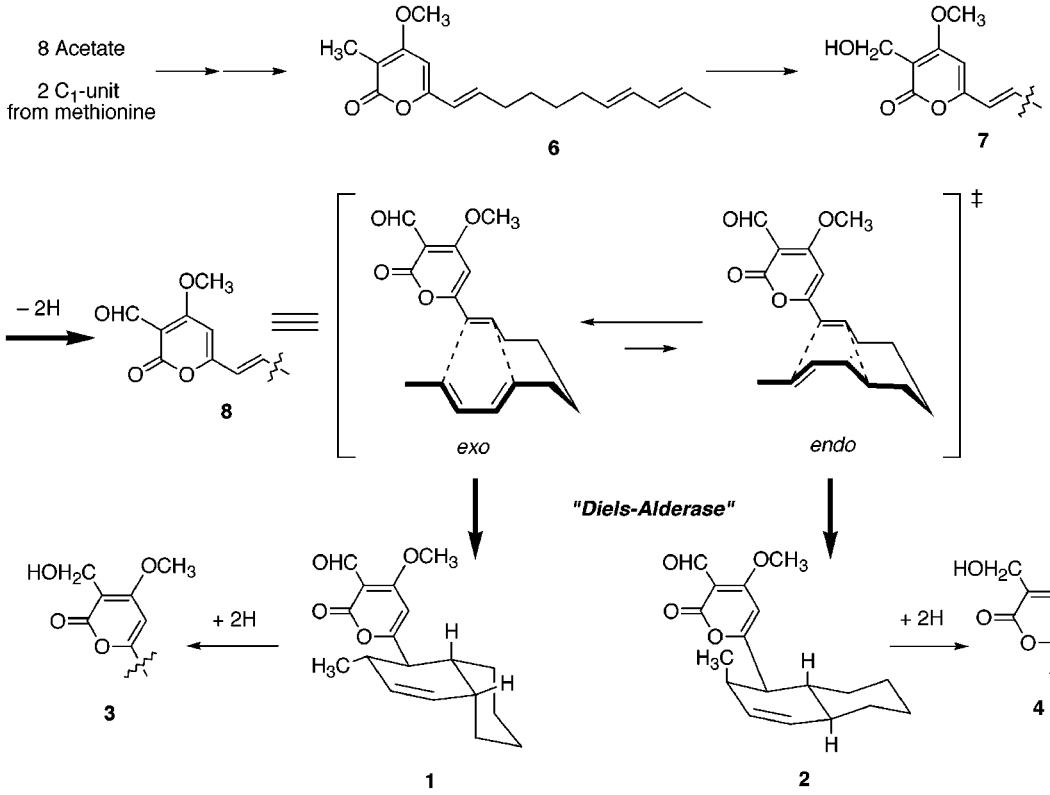
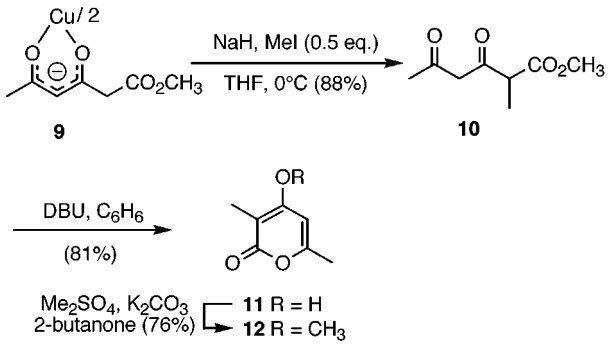
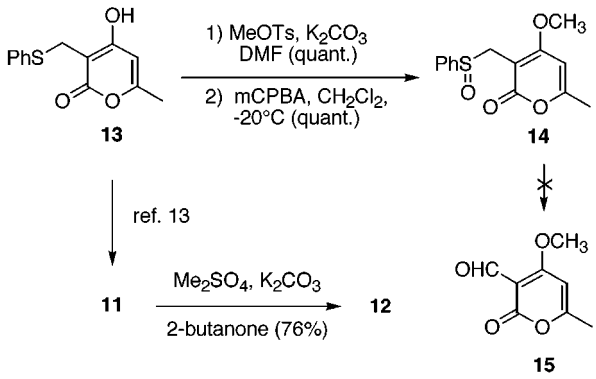
Scheme 1. Biosynthetic Pathway of Solanapyrones[a]



Scheme 2



Scheme 3



condensation yield. In addition, we modified the route which is applicable to the synthesis of multiply labeled compounds for the biosynthetic study of solanapyrones.[5]

First, 3-methyl-2-pyrone **12** was synthesized from the known copper complex **9**[12] (Scheme 2). Following literature precedent,[12] alkylation of **9** with 15 equiv of iodomethane (MeI) under reflux provided the multiply methylated products. The result showed that MeI is highly reactive unlike other alkyl halides tested.[12] Use of MeI (0.5 equiv) at 0 °C predominantly gave the monomethylated product **10** in 88% yield based on MeI. Treatment of the unstable diketoester **10** with DBU followed by O-methylation gave pyrone **12**.

Alternatively, pyrone **12** was synthesized from the known pyrone **13**[13] via **11** by desulfurization and methylation (Scheme 3). Transformation of **13** to formylpyrone **15** was then attempted. Methylation with methyl *p*-toluenesulfonate (TsOMe) followed by oxidation with mCPBA gave sulfoxide **14** in quantitative yield. However, Pummerer rearrangements of the sulfoxide **14** under various conditions failed.

Hydroxymethyl-substituted pyrone segments were synthesized as follows (Scheme 4). Starting from pyrone **16**, methylation with TsOMe in the presence of K_2CO_3 followed by $TiCl_4$ mediated formylation[14] and a modified workup procedure gave formylpyrone **15**[14] in improved yield (57%). Reduction of pyrone **15** with $NaBH_4$ and subsequent silylation or tetrahydropyranylation afforded the pyrone segment **19a** or **19b**, respectively.

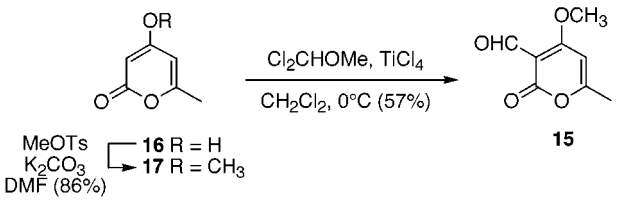
Previously, the synthesis of dienal **21** employed a Li_2-$CuCl_4$-catalyzed cross coupling between the corresponding Grignard reagent and the acetate of sorbic alcohol.[11] The need for multiply labeled prosolanapyrones prompted us to synthesize **21** by an alternative route (Scheme 5) via Wittig reaction between a C_6-aldehyde and a crotyl phosphonium reagent, which would be prepared from

(12) Cervello, J.; Marquet, J.; Mañas, M. M. *Tetrahedron* **1990**, *46*, 2035−2046.

(13) The pyrone **13** was prepared by condensation of formaldehyde, thiophenol, and commercially available pyrone **16**, see: Mañas, M. M.; Pleixats, R. *Synthesis* **1984**, 430−431.

(14) Poulton, G. A.; Cyr, T. D. *Can. J. Chem.* **1982**, *60*, 2821−2829.

Scheme 4



Scheme 5

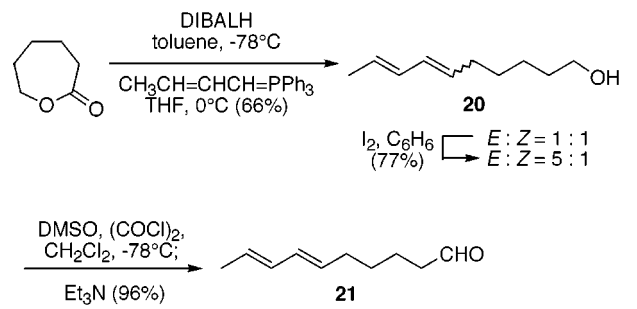
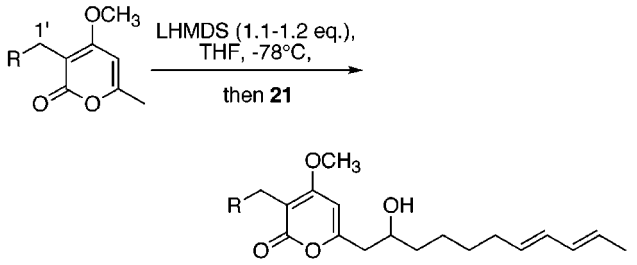


Table 1. Aldol Reactions of Various 3-Substituted Pyrones



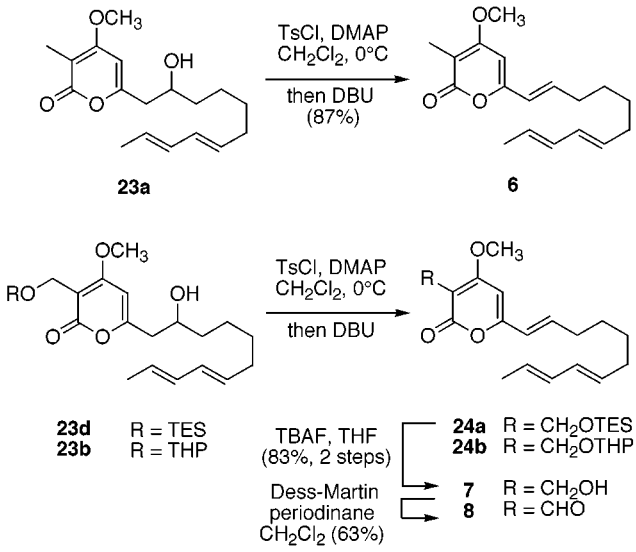
substrate	R	yield (%)	recovered SM (%)[a]	product
12	H	66	0	**23a**
19b	OTHP	28	0	**23b**
22	SPh	17	trace	**23c**
19a	OTES	17	26	**23d**
18	OH	10	0	**23e**

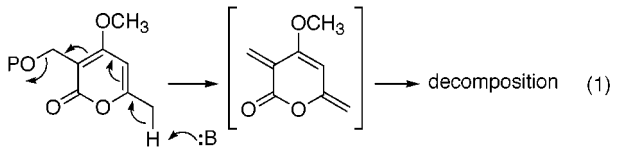
[a] SM = starting material. [b] Base (2.2 equiv), −10 °C.

propargyl alcohol via alkylation and reduction of the alkyne. Starting from ϵ-caprolactone, dienol **20** was synthesized in an one-pot manner. In the event, treatment of a toluene solution of the lactone with DIBALH at −78 °C resulted in the corresponding hemiacetal which was reacted with the phosphorane prepared from crotyl triphenylphosphonium bromide and *n*-BuLi at 0 °C to afford a 1:1 mixture of *E*,*E*- and *E*,*Z*-dienols **20** in 66% yield. Isomerization with I_2 to improve the *E*,*E*-:*E*,*Z*-ratio to 5:1, and Swern oxidation furnished dienal **21**.

With the pyrone and dienal segments in hand, the aldol reactions between various 2-pyrones and *E*,*E*-dienal **21** were examined. The reaction of 3-methyl-2-pyrone **12** proceeded smoothly to yield the adduct **23a** as a single product (Table 1). On the other hand, in the case of the pyrones with the substituent at C-1′, the yields of the reactions did not exceed 30%. In the reaction of the THP-protected pyrone **19b**, 2*H*-tetrahydropyran-2-ol was formed as a byproduct. This indicated that an elimination competed with enolate formation as shown in eq 1. To

Scheme 6





suppress the elimination, the reaction with the dianion prepared from **18** and use of in situ protection[15] of aldehyde **15** with lithium *N*-methyl-*N*-(2-pyridyl)amide or lithium *N*-methylpiperazide were tested. All attempts, however, could not improve the yield.[16]

Transformation of the aldol adducts to prosolanapyrones was employed as shown in Scheme 6. Tosylation of **23a** and subsequent elimination with DBU provided prosolanapyrone I (**6**) in 87% yield. Similarly, adduct **23b** was converted to the unsaturated product **24b**. The deprotection of the THP-protected pyrone **24b** was problematic as deprotection under usual conditions (PPTS in MeOH at 60 °C) failed and harsher conditions (2 M HCl, EtOH, reflux) caused decomposition. When PPTS-catalyzed acid hydrolysis of the *tert*-butyldiphenylsilyl group protected pyrone **25** was attempted, the methyl ether **26** was obtained in low yield. This result suggests

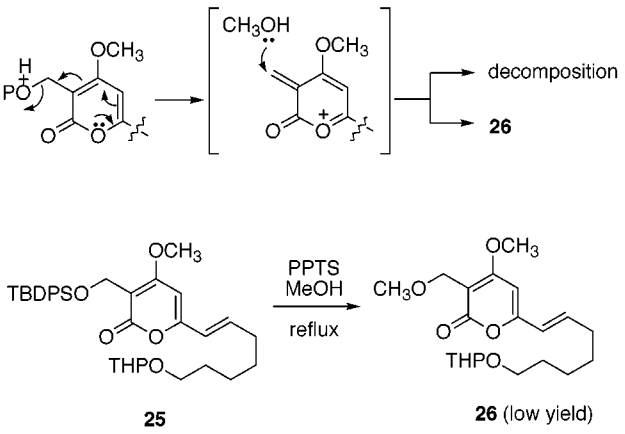
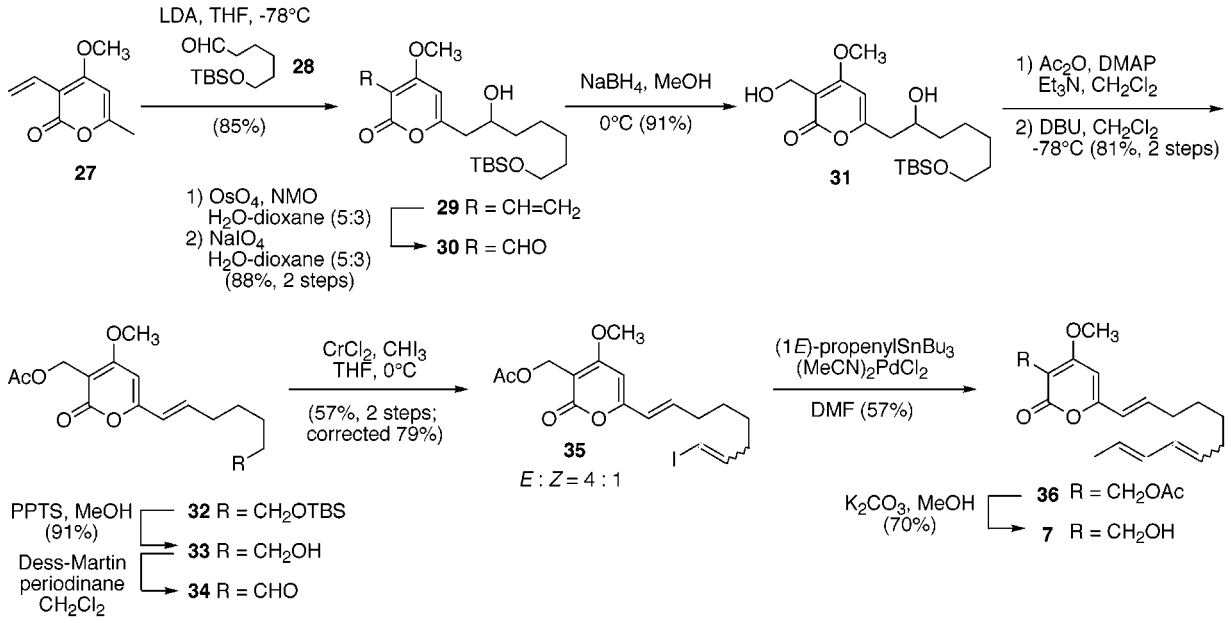


Figure 1.

Scheme 7



that cleavage the removal of the C-1′−O bond occurred under acidic conditions and was followed by either addition of MeOH or decomposition (Figure 1). Among the protecting groups tested (THP, SEM, and TES), the TES group gave the best result. Thus, tosylation−elimination of **23d** followed by desilylation provided prosolanapyrone II (**7**) in 83% overall yield. Oxidation of **7** with Dess−Martin periodinane[17] furnished prosolanapyrone III (**8**) in 63% yield.

Improved Synthesis of Prosolanapyrone II. The observation that 3-methyl-2-pyrone (**12**) gave adduct **23a** in a good yield prompted us to use 3-vinyl-2-pyrone (**27**),[11] which would allow subsequent conversion to the hydroxymethyl derivative. Indeed, the reaction of **27** with aldehyde **28** prepared from hexan-1,6-diol in two steps proceeded smoothly to give adduct **29** in 85% yield (Scheme 7). Oxidative cleavage of the terminal olefin was employed in a two-step manner [(1) OsO_4, *N*-methylmorpholine *N*-oxide, (2) $NaIO_4$] to afford aldehyde **30**. After reduction and subsequent acetylation of the resultant diol **31**, elimination of the secondary acetoxy group with DBU provided olefin **32** in good overall yield (70%, five steps).

To introduce the diene moiety into the side chain, the terminal alkoxy group in **32** was converted to vinyl iodide in **35** as follows. After deprotection of the silyl group, oxidation followed by Takai reaction[18] afforded a 4:1 mixture of *E*- and *Z*-vinyl iodide **35**. Efforts to increase *E*-selectivity by changing solvents[19,20] and temperature were unsuccessful likely due to instability of the pyrone moiety. A Stille reaction[21] of **35** with 1-propenyltributylstannane prepared from (*E*)-1-bromopropene gave the diene **36**, which was finally converted to prosolanapyrone II (**7**) by alkaline hydrolysis.

Table 2. Nonenzymatic Diels−Alder Reactions of Prosolanapyrones[a]

entry	substrate	solvent	reaction time	yield (%)	recovery of SM (%)	endo/exo
1	**6**	toluene	48 h	12	11	1.9
2	**6**	H_2O	7 d	7	93	>10
3	**7**	toluene	48 h	55	2	2.2
4[b]	**7**	$CHCl_3$	2 h	7	91	3.6
5[b]	**7**	CH_3CN	24 h	71	18	5.6
6	**7**	H_2O	2 d	19	81	20
7	**8**	toluene	1 h	68	27	2.7
8	**8**	$CHCl_3$	1 h	64	28	3.4
9	**8**	CH_3CN	1 h	82	10	4.4
10	**8**	H_2O	3 h	62	28	23

[a] All reactions were carried out at 110 °C except entries 1 (180 °C) and 2, 6, and 10 (30 °C). [b] Prolonged reaction time caused degradation of products.

Nonenzymatic Diels−Alder Reaction of Prosolanapyrones. To assess the diastereoselectivity and the intrinsic reactivity of prosolanapyrones, Diels−Alder reactions were examined under various conditions. The results are shown in Table 2. Endo-/exo-selectivities with **6**−**8** were essentially the same in various solvents while the endo-selectivity was increased with increasing solvent polarity. The slight preference of endo-selectivity in less polar solvents suggest that there is little steric congestion, in both endo- and exo-transition states as reported in the reactions of simple decatriene systems.[22]

In less polar solvents, heating was required for the effective cycloaddition of all three compounds. Rate acceleration depended on the oxidation level of the 3-substituent in prosolanapyrones (Table 2). These are explained by the LUMO energy of the dienophile moiety

(15) Comins, D. L. *Synlett* **1992**, 615−625.
(16) Due to the low solubility of the pyrones, we could not test other solvents.
(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. For preparation of Dess−Martin periodinane, see: Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
(18) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.
(19) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513.
(20) Following Evans modification,[19] the model reaction using decanal was employed in dioxane/THF (6:1) in the presence of pyrone **19a**, we could improve an isomer ratio of the vinyl iodide (E/Z = 19:1) but none of **19a** was recovered. We found that iodine liberated during the reaction caused decomposition of the pyrone moiety in removal of solvent. However, we could not identify other factors for the decomposition.
(21) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417−6422.
(22) Raimondi, L.; Brown, F. K.; Gonzalez, J.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 4796−4804.

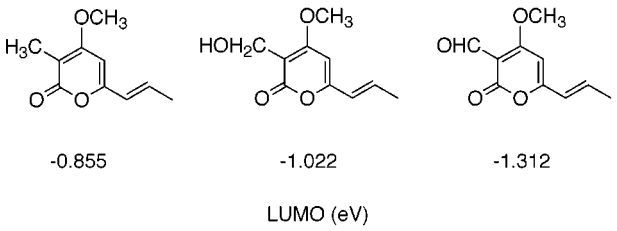


Figure 2. LUMO energies of prosolanapyrone analogues. Calculated by MOPAC 6.0 with PM3.

in the pyrones (Figure 2). Use of Lewis acid (1 equiv of Et_2AlCl, CH_2Cl_2, −78 °C to rt) caused simply degradation of starting materials in the case of **6** and **8**. We noted a significant rate acceleration of prosolanapyrone III (**8**) in aqueous medium. The increased reactivity could be explained by "hydrophobic effect"[23] and/or hydrogen bonding[24] between water and the dienophile carbonyl group. To our knowledge, this enormous rate acceleration in the reaction of decatrienes has not been reported previously. Since there are numbers of natural products with trans-fused decalin ring systems,[25] it could be useful that proper modification of the dienophile, such as introducing a reactive electron-withdrawing group, would result in predominant formation of trans-fused decalin systems with rate acceleration. We chose **7** as a substrate to study the enzymatic Diels−Alder reaction, to suppress the nonenzymatic reaction which reduces the optical purity of **1**.

Enzymatic Diels−Alder Reaction of Prosolanapyrone II. In an analytical-scale experiment, the crude enzyme containing the solanapyrone synthase provided (−)-**1** with excellent enantioselectivity (99% ee) and relatively high exo-selectivity (6:1).[7] During optimizing reaction conditions, we found that the reactions in semipreparative scale were not reproducible and provided solanapyrones with low enantio- and diastereoselectivity. This is mainly due to the fact that cycloaddition activity was lost more rapidly than oxidation activity and this caused accumulation of **8**. Addition of 30% glycerol[8] was not enough to prolong the cycloaddition activity. Use of catalase to remove coproduct hydrogen peroxide, which might inactivate the enzyme, did not affect the reaction rate or selectivity. Finally, we found that freezing in liquid nitrogen of the freshly prepared enzyme containing 30% glycerol is effective for maintaining activity for months.

The hydrophobic nature of **7** prompted us to examine the effect of substrate concentration of the substrate on enzyme activity. A substrate concentration range of 0.05−0.75 mM was tested, without any loss of reaction rate or stereoselectivity. Since reactions are performed under relatively dilute conditions, normal workup such as solvent extraction or lyophilization was a major disadvantage of the enzymatic reaction. We found that hydrophobic resin HP-20 adsorbed both substrate and products, and the adsorbed materials were easily eluted with ethyl acetate, simplifying products recovery.

Using the enzyme preparation shown above, a 5:1 mixture of 7″*E*,9″*E*- and 7″*Z*,9″*E*-**7** at 0.75 mM was converted to a 6:1 mixture of solanapyrones A (**1**) and D (**2**) in 61% yield with >98 and 67% ee,[26] respectively, and 10% of prosolanapyrone III (**8**) recovered (eq 2). For our purpose, contamination with the hardly separable *Z*-isomer of substrate **7** was not a problem since the corresponding *E*,*Z*-isomer of **8** was not cyclized under the reaction conditions. On the basis of the chromatographic behavior of the enzyme,[8] we proposed that the single enzyme catalyzes the oxidation from the alcohol **7** to the reactive aldehyde **8** which is further converted to the adducts **1** and **2** by the Diels−Alder reaction. Erosion of the ee of **2** may be due to the partially distorted conformation of the bifunctional enzyme. Thus, as **8** is released from the active site, it is then converted to (±)-**2** by the nonenzymatic Diels−Alder reaction.

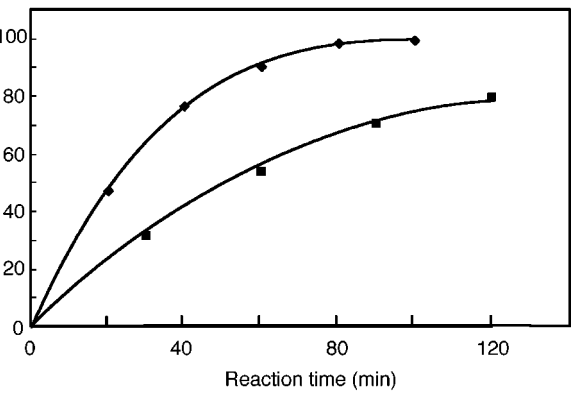
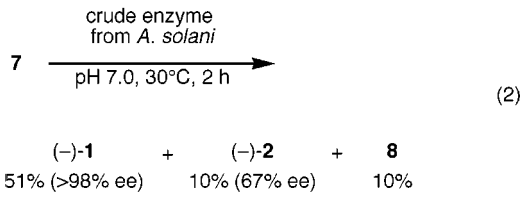


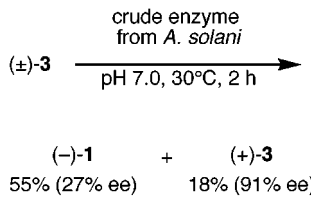
Figure 3. Enzymatic kinetic resolution of (−)- and (±)-solanapyrone B (**3**).



Kinetic Resolution of (±)-Solanapyrone B. During the enzymatic study, we found that the crude enzyme containing solanapyrone synthase catalyzes not only the oxidation of prosolanapyrone II (**7**) to III (**8**) but that of solanapyrone B (**3**) to A (**1**) in the presence of oxygen. The same enzyme preparation converted 84% of (−)-**3** to afford (−)-**1** compared with the conversion of **7** as a control. On the basis of this result, we anticipated that the enzyme, prior to the oxidation, has a transition states structure of **7** similar to those of Diels−Alder reaction adduct. If so, the enzyme would oxidize racemic **3** with different rates. Thus, we employed kinetic resolution of (±)-solanapyrone B (**3**).

First, the enzymatic reaction rates of (−)-**3** and (±)-**3** prepared in the thermal cycloaddition of **7** were examined (Figure 3). As expected, (−)-**3** was oxidized more rapidly than (±)-**3** but the difference between them was relatively small. In larger scale incubation (30 °C, 2 h), (−)-**1** was obtained in 55% yield with 27% ee and (+)-**3** was recovered in 18% yield with 91% ee (eq 3). This kinetic resolution allowed us to obtain the unnatural form of solanapyrone B (**3**).

(23) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 159−164.
(24) Ruiz-López, M. F.; Assfeld, X.; García, J. I.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1993**, *115*, 8780−8787.
(25) Ichihara, A.; Oikawa, H. *Curr. Org. Chem.* **1998**, *2*, 365−394.
(26) Suzuki, E. *Synthesis* **1978**, 144−146.



Conclusion. Convergent, efficient syntheses of prosolanapyrones via the aldol reactions of pyrone and dienal segments are described. Through these syntheses, we found that 3-alkoxymethyl-substituted 2-pyrones were labile under both acidic and basic conditions. This drawback was overcome by the proper choice of protecting group and use of vinylpyrone **27**. Enzymatic Diels−Alder reaction of **7** on semipreparative scale afforded (−)-**1** without loss of enantio- and diastereoselectivity. We also showed an enzymatic kinetic resolution of (±)-**3** furnished unnatural (+)-**3**. Our synthetic approaches to prosolanapyrones allow syntheses of various analogues which would be useful for the study of the substrate specificity of the Diels−Alderase. Despite current unavailability of large amounts of solanapyrone synthase, use of the enzyme for the enantioselective construction of the cis-fused decalin system has greatly simplified the synthetic route of (−)-**1**. This approach would be practical when information on amino acid sequence and the gene encoding the enzyme is cloned and overexpressed.

Currently, solanapyrone synthase is proposed to be an oxidase which provides the reactive aldehyde **8** and catalyzes cycloaddition. This implicates that some oxidases or dehydrogenases could be good sources of Diels−Alderase as a bifunctional enzyme when they can provide reactive dienophile species and stabilize them as transition states.

Experimental Section

General Methods. Unless otherwise noted, nonaqueous reactions were carried out under argon atmosphere. Tetrahydrofuran (THF) and toluene were distilled from sodium metal/benzophenone ketyl. Benzene, CH_2Cl_2, *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide, and triethylamine were distilled from calcium hydride and were stored under argon atmosphere. Methanol was distilled from magnesium methoxide. Dess−Martin periodinane[17] was prepared according to literature procedures. All other commercially obtained reagents were used as received. Melting points are uncorrected. The enzyme preparation containing solanapyrone synthase was prepared as described.[8] The specific activity of the enzyme was 0.096 mU/μL (one unit will convert 1 mmol of **7** per min at 30 °C to **1**, **2**, and **8**).

Methyl 2-Methyl-3,5-diketohexanoate (10). To a solution of copper complex **9** (12.8 g, 32 mmol) in THF (384 mL) was added NaH (40% in mineral oil, 1.28 g, 32 mmol). After 1 h of stirring at ambient temperature, iodomethane (2.05 mL, 32 mmol) was added dropwise at 0 °C. The mixture was stirred at ambient temperature for 20 h before the reaction was quenched with 1 M HCl and extracted with CH_2Cl_2 The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (hexane/acetone, 7:1) gave copper-decomplexed methyl 3,5-diketohexanoate (5.19 g) and ester **10** (4.97 g, 88% based on iodomethane) as a colorless oil: IR (KBr) 1742, 1610 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.37 (d, 3H, J = 8.0 Hz), 2.04, (s, 3H), 3.36 (d, 1H, J = 8.0 Hz), 3.70 (s, 3H), 5.52, (s, 1H); FI-MS m/z 172 (M^+); FI-HR-MS calcd for $C_8H_{12}O_4$ 172.1809 (M^+), found m/z 172.1807.

4-Hydroxy-3,6-dimethyl-2*H*-pyran-2-one (11). To a solution of ester **10** (53 mg, 0.31 mmol) in benzene (1 mL) was added DBU (48 mg, 0.31 mmol). The mixture was stirred under reflux for 1h. After being cooled to ambient temperature, 1 M HCl was added and the resulting solution was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was crystallized from $CHCl_3$ and MeOH to afford hydroxypyrone **11** (35 mg, 81%) as white crystals: mp 205−207 °C, (lit.[13] 209−211 °C); ^{1}H NMR (90 MHz, $CDCl_3$ + CD_3OD) δ 1.86 (s, 3H), 2.20 (s, 3H), 5.90 (s, 1H).

4-Methoxy-3,6-dimethyl-2*H*-pyran-2-one (12). To a solution of hydroxypyrone **11** (104 mg, 0.47 mmol) in 2-butanone (20 mL) were added K_2CO_3 (0.93 g, 6 mmol) and dimethyl sulfate (0.054 mL, 0.55 mmol). The mixture was stirred for 3.5 h under reflux. It was cooled to ambient temperature and filtered. After concentration of the solution in vacuo, the residue was purified by silica gel flash chromatography ($CHCl_3$/acetone, 95:5) to give methoxypyrone **12** (91.7 mg, 81%) as white crystals: mp 87−89 °C (from $CHCl_3$), lit.[13] 82−83 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.26 (s, 3H), 3.88 (s, 3H), 6.03 (s, 1H).

4-Methoxy-6-methyl-2*H*-pyran-2-one (17). To a solution of hydroxypyrone **16** (7.3 g, 58 mmol) in DMF (290 mL) were added K_2CO_3 (16 g, 116 mmol) and methyl *p*-toluenesulfonate (22 g, 116 mmol) at 3 °C. The mixture was allowed to warm to ambient temperature. After 12 h of stirring, the mixture was poured into water and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was crystallized from EtOAc to afford methoxypyrone **17** (5.00 g) as white crystals. The mother liquor was concentrated in vacuo and purified by silica gel flash chromatography ($CHCl_3$/acetone, 4:1) to give **17** (1.54 g, total 79%) as white crystals: mp 86 °C (from EtOAc), (lit.[26] 86−87.5 °C); IR (KBr) 1710 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.20 (br s, 3H), 3.79 (s, 3H), 5.40 (d, 1H, J = 2.0 Hz), 5.77 (br d, 1H, J = 2.0 Hz); EI-MS m/z 140 (M^+); EI-HR-MS calcd for $C_7H_8O_3$ m/z 140.0473 (M^+), found 140.0471.

3-Formyl-4-methoxy-6-methyl-2*H*-pyran-2-one (15). To a solution of **17** (5.8 g, 41.6 mmol) in CH_2Cl_2 (40 mL) was added $TiCl_4$ (46 mL, 416 mmol). Under ice-cooled conditions, dichloromethyl methyl ether (37 mL, 416 mmol) was added over 30 min with stirring, and evolved HCl was removed by continuous nitrogen flow. The mixture was allowed to warm to ambient temperature and stirred for 6 h. The mixture was carefully poured into crushed ice, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/acetone, 4:1) gave formylpyrone **15** (4.0 g, 57%) and starting material **17** (0.5 g, 9%). For **15**: yellow crystals: mp 172−175 °C; IR (KBr) 1750 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.30 (br s, 3H), 4.01 (s, 3H), 6.18 (s, 1H), 10.06 (s, 1H); EI-MS m/z 168 (M^+); EI-HR-MS calcd for $C_8H_8O_4$ m/z 168.0422 (M^+), found 168.0442.

3-(Hydroxymethyl)-4-methoxy-6-methyl-2*H*-pyran-2-one (18). To a solution of formylpyrone **15** (2.76 g, 16.4 mmol) in MeOH (150 mL) was added $NaBH_4$ (1.59 g, 49.2 mmol) at 3 °C. After the mixture was stirred for 1 h, the excess reagent was quenched with acetone. The volatile materials were removed in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/acetone, 4:1) gave alcohol **18** (2.34 g, 84%) as white crystals: mp 149−151 °C; IR (KBr) 3406, 1683 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.90 (t, 1H, J = 5.9 Hz), 3.90 (s, 3H), 4.54 (d, 2H, J = 5.9 Hz), 6.05 (s, 1H); EI-MS 170 (M^+); EI-HR-MS calcd for $C_8H_{10}O_4$ m/z 170.0579, found 170.0606 ((M^+).

3-[[1-(Triethylsilyl)oxy]methyl]-4-methoxy-6-methyl-2*H*-pyran-2-one (19a). To a solution of alcohol **18** (2.34 g, 13.8 mmol) in CH_2Cl_2 (200 mL) was added 2,6-lutidine (5.1 mL, 44 mmol). Under ice-cooled conditions, triethylsilyl trifluoromethanesulfonate (4.7 mL, 21 mmol) was added dropwise. After 1 h of stirring, the mixture was poured into brine and aqueous layer was separated and extracted with

CH_2Cl_2. The combined organic extracts were washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, successively, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/EtOAc, 9:1) gave silyl ether **19a** (2.94 g, 75%) as white crystals: mp 111−112 °C (from $CHCl_3$); IR (KBr) 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.57 (q, 6H, J = 7.92 Hz), 0.88 (t, 9H, J = 7.92 Hz), 2.18 (s, 3H), 3.83 (s, 3H), 4.45 (s, 2H), 5.98 (s, 1H); EI-MS m/z 255 (M^+ − Et); EI-HR-MS calcd for $C_{12}H_{19}O_4Si$ (M^+ − Et) m/z 255.1052, found 255.1045.

(6*E*,8*E*)-6,8-Decadienol (20). To a solution of ϵ-caprolactone (3.5 mL, 31.5 mmol) in THF (60 mL) was added dropwise DIBALH (1.0 M THF solution, 33.3 mL, 33.3 mmol) at −78 °C. After 45 min of stirring, it was transferred via cannula to a solution prepared with 2-butenyltriphenylphosphonium bromide (15 g, 37.8 mmol) in THF (60 mL) and *n*-BuLi (1.6 M THF solution, 22.5 mL, 36.0 mmol) at 3 °C. After the mixture was allowed to warm to ambient temperature and stirred for 2 h, saturated aqueous NH_4Cl was added. The mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (hexane/ether, 5:1) gave dienol **20** (3.20 g, 66%, (6*E*,8*E*):(6*E*,8*Z*) = 1:1).

To a solution of dienol **20** (2.56 g, 16.7 mmol) in benzene (72 mL) was added iodine (115 mg, 91 mmol). The mixture was stirred avoiding light for 24 h before the reaction was quenched with saturated aqueous $Na_2S_2O_3$. After 15 min of stirring, the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification of the resultant oil ((6*E*,8*E*):(6*E*,8*Z*) = 5:1) by 15% $AgNO_3$/silica gel chromatography (hexane/ether, 95:5) gave (6*E*,8*E*)-dienol **20** (0.66 g, 29%) and a (6*E*,8*Z*)- and (6*E*,8*E*)-mixture (1.40 g, 55%) which was subjected to additional isomerization and recovery of **20**. For the (6*E*,8*E*)-isomer: a colorless oil; IR (KBr) 970 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.34−1.47 (m, 4H), 1.57 (m, 2H), 1.72 (d, 3H, J = 6.6 Hz), 2.06 (m, 2H), 3.63 (t, 2H, J = 6.6 Hz), 5.48−5.63 (m, 2H), 5.94−6.07 (m, 2H); EI-MS m/z 154 (M^+); EI-HR-MS calcd for $C_{10}H_{18}O$ (M^+) 154.1358, found 154.1352.

(6*E*,8*E*)-6,8-Decadienal (21). To a solution of oxalyl chloride (0.28 mL, 3.2 mmol) in CH_2Cl_2 (10 mL) was added DMSO (0.32 mL, 4.5 mmol) in CH_2Cl_2 (10 mL) at −78 °C. After the mixture was stirred for 10 min, **20** (250 mg, 1.62 mmol) in CH_2Cl_2 (5 mL) was introduced, and the resulting mixture was stirred for 20 min. Triethylamine (1.7 mL, 12.2 mmol) was added, and the mixture was allowed to warm to ambient temperature and stirred for 30 min. The reaction was quenched with water, and the aqueous layer was separated and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography (hexane/ether, 9:1) gave dienal **21** (210 mg, 85%) as a colorless oil: IR (KBr) 1710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.36−1.47 (m, 2H), 1.58−1.69 (m, 2H), 1.72 (d, 3H, J = 6.6 Hz), 2.07 (m, 2H), 2.42 (m, 2H), 5.46−5.64 (m, 2H), 5.94−6.05 (m, 2H), 9.75 (dd, 1H, J = 2.0, 1.3 Hz); EI-MS m/z 152 (M^+); EI-HR-MS calcd for $C_{10}H_{16}O$ (M^+) m/z 152.1201, found 15.1221.

6-[(7*E*,9*E*)-2-Hydroxy-7,9-undecadienyl]-4-methoxy-3-methyl-2*H*-pyran-2-one (23a). To a solution of LDA in THF (2.2 mL) (generated from *n*-BuLi (1.6 M hexane solution, 1.33 mL, 1.99 mmol) and *N*,*N*-diisopropylamine (0.32 mL, 2.29 mmol) at 0 °C) at −78 °C was added dropwise pyrone **12** (273 mg, 1.74 mmol) in THF (6 mL) over 50 min. A solution of dienal **21** (289 mg, 1.9 mmol) in THF (6.3 mL) was added dropwise, and the mixture was stirred for 4 h before saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography ($CHCl_3$/acetone, 95:5) gave adduct **23a** (350 mg, 66%) as a colorless oil: IR (KBr) 3350, 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.27−1.56 (m, 6H), 1.73 (d, 3H, J = 5.9 Hz), 1.91 (s, 3H), 2.04−2.10 (m, 2H), 2.52 (dd, 1H, J = 9.2, 14.5 Hz), 2.69 (dd, 1H, J = 3.3, 14.5 Hz), 3.88 (s, 3H), 4.06 (m, 1H), 5.49−5.61 (m, 2H), 5.94−6.03 (m, 2H), 6.10 (s, 1H); EI-MS m/z 306 (M^+); EI-HR-MS calcd for $C_{18}H_{26}O_4$ (M^+) m/z 306.1831, found 306.1840.

Prosolanapyrone I (6). To a solution of adduct **23a** (50 mg, 0.161 mmol) in CH_2Cl_2 (3 mL) were added DMAP (203 mg, 1.61 mmol) and *p*-toluenesulfonyl chloride (79 mg, 0.40 mmol). The mixture was stirred for 24 h at ambient temperature. To this was added DBU (304 mg, 0.59 mmol). After an additional 4 h of stirring, the mixture was diluted with CH_2Cl_2. The resultant mixture was washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, successively, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel column chromatography (hexane/ether, 9:1) gave **6** (41 mg, 87%) as a colorless oil: IR (KBr) 3400, 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.40−1.49 (m, 6H), 1.72 (d, 3H, J = 6.6 Hz), 1.93 (s, 3H), 2.02−2.10 (m, 2H), 2.17−2.22 (m, 2H), 3.87 (s, 3H), 5.50−5.61 (m, 2H), 5.92−6.03 (m, 3H), 6.11 (s, 1H), 6.07 (dt, 1H, J = 7.3, 15.2 Hz); EI-MS m/z 288 (M^+); EI-HR-MS calcd for $C_{18}H_{24}O_3$ (M^+) m/z 288.1726, found 288.1727.

3-[[1-(Triethylsilyl)oxy]methyl]-6-[(7*E*,9*E*)-2-hydroxy-7,9-undecadienyl]-4-methoxy-2*H*-pyran-2-one (23d). To a solution of pyrone **19a** (515 mg, 1.78 mmol) in THF (20 mL) at −78 °C was added dropwise LHMDS (1.0 M THF solution, 2.55 mL, 2.55 mmol) over 10 min. After 15 min, a solution of dienal **21** (310 mg, 2.01 mmol) in THF (6.3 mL) was added dropwise, and the mixture was stirred for 1 h before saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/acetone, 9:1) and then preparative thin layer silica gel chromatography ($CHCl_3$/acetone, 6:1) gave adduct **23d** (134 mg, 17%) as a colorless oil and the starting materials **19a** (82 mg, 16%) and **21** (56 mg, 18%). For **23d**: IR (KBr) 3400, 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.64 (q, 6H, J = 7.9 Hz), 0.95 (t, 9H, J = 7.9 Hz), 1.38−1.50 (m, 6H), 1.72 (d, 3H, J = 5.9 Hz), 2.06 (m, 2H), 2.51 (dd, 1H, J = 8.6, 14.5 Hz), 2.66 (dd, 1H, J = 4.0, 14.5 Hz), 3.89 (s, 3H), 4.04 (m, 1H), 4.51 (s, 2H), 5.49−5.61 (m, 2H), 5.97−6.05 (m, 2H), 6.11 (s, 1H); EI-MS m/z 407 (M^+ − Et); EI-HR-MS calcd for $C_{22}H_{35}O_5Si$ (M^+ − Et) m/z 407.2250, found 407.2250.

Prosolanapyrone II (7). To a solution of adduct **23d** (20 mg, 0.046 mmol) in CH_2Cl_2 (0.25 mL) were added DMAP (84 mg, 0.69 mmol) and *p*-toluenesulfonyl chloride (26 mg, 0.14 mmol). The mixture was stirred for 30 min at ambient temperature. To this was added DBU (90 mg, 0.59 mmol), and the resulting mixture was stirred for further 1 h before dilution with EtOAc. The resultant mixture was washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, successively, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude unsaturated product thus obtained was used without further purification.

To a solution of the product above in THF (0.3 mL) was added Bu_4NF (1.0 M THF solution, 0.06 mL, 0.06 mmol). The mixture was stirred at ambient temperature for 30 min before the mixture was diluted with EtOAc. The resultant mixture was washed with saturated aqueous NH_4Cl and brine, successively, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative thin-layer silica gel chromatography (hexane/EtOAc, 1:2) gave **7** (12 mg, 83%) as a colorless oil: IR (KBr) 3400, 1680 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.34−1.55 (m, 4H), 1.73 (d, 3H, J = 6.6 Hz), 2.04−2.11 (m, 2H), 2.23−2.2.25 (m, 2H), 2.90 (dd, 1H, J = 6.6, 7.3 Hz), 3.90 (s, 3H), 4.55 (d, 2H, J = 6.6, d, J = 7.3 Hz), 5.50−5.62 (m, 2H), 5.96−6.03 (m, 3H), 6.00 (s, 1H), 6.78 (dt, 1H, J = 7.4, 15.2 Hz); EI-MS m/z 304 (M^+); EI-HR-MS calcd for $C_{18}H_{24}O_4$ (M^+) m/z 304.1674, found 304.1686.

Prosolanapyrone III (8). To a solution of **7** (5.7 mg, 19 mmol) in CH_2Cl_2 (0.2 mL) was added Dess−Martin periodinane (14 mg). The mixture was stirred at ambient temperature for 2 h, when saturated aqueous Na_2CO_3 and saturated aqueous $Na_2S_2O_3$ was added. The resultant mixture was

stirred for 10 min and then extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried by passing through a short column of anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by preparative thin-layer silica gel chromatography (hexane/EtOAc, 1:2) gave **8** (3.5 mg, 63%) and the starting material **7** (1.2 mg, 21%). For **8**: a colorless oil: IR (KBr) 1732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.42−1.54 (m, 4H), 1.73 (d, 3H, J = 5.9 Hz), 2.04−2.12 (m, 2H), 2.26−2.2.33 (m, 2H), 4.06 (s, 3H), 5.47−5.63 (m, 2H), 5.98−6.08 (m, 3H), 6.03 (s, 1H), 7.01 (dt, 1H, J = 7.3, 15.2 Hz), 10.15 (s, 1H); EI-MS m/z 302 (M^+); EI-HR-MS calcd for $C_{18}H_{22}O_4$ (M^+) m/z 302.1518, found 302.1535.

6-[2-Hydroxy-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-heptyl]-4-methoxy-3-vinyl-2*H*-pyran-2-one (29). To a solution of pyrone **27** (1.62 g, 9.85 mmol) in THF (50 mL) was added dropwise LHMDS (1.5 M hexane solution, 9.85 mL, 14.7 mmol) at −78 °C over 10 min. To this was added dropwise the aldehyde **28** (4.85 g, 19.7 mmol) in THF (25 mL) over 20 min. After 70 min, additional **28** (2.42 g, 9.85 mmol) in THF (12 mL) was added, and the mixture was stirred for 2 h before saturated aqueous NH_4Cl was added. The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/EtOAc, 9:1) gave adduct **29** (3.29 g, 85%) as a colorless oil: IR (KBr) 3371, 1684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.89 (s, 9H), 1.30−1.60 (m, 8H), 2.54 (dd, 1H, J = 8.9, 14.9 Hz), 2.70 (dd, 1H, J = 3.6, 14.5 Hz), 3.61 (t, 2H, J = 6.3 Hz), 3.93 (s, 3H), 4.10 (m, 1H), 5.35 (dd, 1H, J = 2.3, 11.9 Hz), 6.16 (s, 1H), 6.25 (dd, 1H, J = 2.3, 17.8 Hz), 6.72 (dd, 1H, J = 11.9, 17.8 Hz); EI-MS m/z 381 ($M^+ - CH_3$); EI-HR-MS calcd for $C_{20}H_{33}O_5Si$ ($M^+ - CH_3$) m/z 381.2097, found 381.2126.

3-Formyl-6-[7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-(hydroxyheptyl)]-4-methoxy-2*H*-pyran-2-one (30). To a solution of adduct **29** (120 mg, 0.293 mmol) in H_2O/dioxane (11 mL, 5:3) were added $K_2OsO_4 \cdot 2H_2O$ (1.1 mg, 0.003 mmol) in water (0.02 mL) and *N*-methylmorpholine *N*-oxide (68 mg, 0.581 mmol). The mixture was stirred overnight at ambient temperature before the mixture was quenched with 5% aqueous $Na_2S_2O_3$. The resultant mixture was stirred for further 30 min. To this was added saturated aqueous NH_4Cl, and the resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude diol thus obtained was used without further purification.

To a solution of the diol prepared above in H_2O/dioxane (11 mL, 5:3) was added sodium metaperiodate (94 mg, 0.439 mmol). The mixture was stirred at ambient temperature for 1.5 h and then extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/MeOH, 20:1) gave formylpyrone **30** (108 mg, 2 steps, 88%) as a colorless oil: IR (KBr) 3373, 1733, 1685 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.88 (s, 9H), 1.30−1.70 (m, 8H), 2.59 (dd, 1H, J = 9.2, 14.5 Hz), 2.74 (dd, 1H, J = 2.6, 14.5 Hz), 3.61 (t, 2H, J = 5.9 Hz), 4.06 (s, 3H), 4.10 (m, 1H), 6.25 (s, 1H), 10.1 (s, 1H); EI-MS m/z 365 ($M^+ - (t\text{-Bu} + H_2O)$); EI-HR-MS calcd for $C_{16}H_{23}O_5Si$ ($M^+ - (t\text{-Bu} - H_2O)$) m/z 323.1315, found 323.1343.

3-(Hydroxymethyl)-6-[7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2-(hydroxyheptyl)]-4-methoxy-2*H*-pyran-2-one (31). To a solution of formylpyrone **30** (58 mg, 0.141 mmol) in MeOH (3 mL) was added $NaBH_4$ (6.2 mg, 0.164 mmol) at 0 °C. The mixture was stirred at ambient temperature for 30 min. To this was added acetone (0.3 mL), and the resultant mixture was diluted with brine and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/MeOH, 20:1) gave diol **31** (53 mg, 91%) as a colorless oil: IR (NaCl) 3389, 1716 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.87 (s, 9H), 1.30−1.70 (m, 4H), 2.03 (s, 6H), 2.74 (d, 2H, J = 5.9 Hz), 3.57 (t, 2H, J = 6.6 Hz), 3.88 (s, 3H), 4.94 (s, 2H), 6.08 (s, 1H), 5.16 (quintet, 1H, J = 6.6 Hz), 6.82 (dt, 1H, J = 6.6, 15.8 Hz); EI-MS m/z 385 ($M^+ - CH_3$); EI-HR-MS calcd for $C_{19}H_{33}O_6Si$ ($M^+ - CH_3$) m/z 385.2015, found 385.2052.

3-(Acetoxymethyl)-6-[(1*E*)-7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]heptenyl]-4-methoxy-2*H*-pyran-2-one (32). To a solution of diol **31** (8.3 mg, 0.020 mmol) in CH_2Cl_2 (0.3 mL) were added DMAP (10.8 mg, 0.082 mmol) and acetic anhydride (0.01 mL, 0.091 mmol) at 0 °C. After 1 h of stirring at ambient temperature, the reaction was quenched with ice and water. The resultant mixture was extracted with $CHCl_3$, and the combined organic layers were washed with 1 M-HCl, saturated aqueous $NaHCO_3$, and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude diacetate thus obtained was used without further purification. For the diacetate: a colorless oil, ^1H NMR (270 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.87 (s, 9H), 1.30−1.70 (m, 4H), 2.03 (s, 6H), 3.57 (t, 2H, J = 6.6 Hz), 3.88 (s, 3H), 4.94 (s, 2H), 6.08 (s, 1H), 5.16 (quintet, 1H, J = 6.6 Hz), 6.82 (dt, 1H, J = 6.6, 15.8 Hz).

To a solution of diacetate prepared above in CH_2Cl_2 (0.3 mL) was added DBU (0.01 mL, 0.065 mmol) at 0 °C. After 40 min of stirring at ambient temperature, the mixture was diluted with 1 M HCl. The resultant mixture was extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel thin-layer chromatography ($CHCl_3$/EtOAc, 15:1) gave olefin **32** (7.6 mg, 81%) as a colorless oil: IR (KBr) 1735, 1698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 1.30−1.60 (m, 4H), 2.05 (s, 3H), 2.24 (ddt, 2H, J = 1.3, 6.6, 7.9 Hz), 3.60 (t, 2H, J = 5.9 Hz), 3.91 (s, 3H), 4.98 (s, 2H), 5.98 (s, 1H), 6.00 (dt, 1H, J = 15.8, 1.3 Hz), 6.82 (dt, 1H, J = 15.8, 6.6 Hz); EI-MS m/z 424 (M^+); EI-HR-MS calcd for $C_{18}H_{27}O_6Si$ ($M^+ - t\text{-Bu}$) m/z 367.1577, found 367.1580.

3-(Acetoxymethyl)-6-[(1*E*)-7-hydroxy-1-heptenyl]-4-methoxy-2*H*-pyran-2-one (33). PPTS (33.9 mg, 0.277 mmol) was added to a solution of olefin **32** (454 mg, 1.07 mmol) in MeOH (30 mL), and the mixture was stirred at ambient temperature for 11 h. To this was added additional PPTS (33.9 mg, 0.277 mmol), and the resultant mixture was stirred for another 24 h before the mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/MeOH, 20:1) gave alcohol **33** (302 mg, 91%) as a colorless oil: IR (KBr) 3378, 1735, 1684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.30−160 (m, 4H), 2.04 (s, 3H), 2.25 (ddt, 2H, J = 1.3, 6.6, 7.3 Hz), 3.64 (t, 2H, J = 5.9 Hz), 3.91 (s, 3H), 4.97 (s, 2H), 5.99 (s, 1H), 6.00 (dt, 1H, J = 15.8, 1.3 Hz), 6.80 (dt, 1H, J = 15.8, 6.6 Hz); EI-MS m/z 310 (M^+); EI-HR-MS calcd for $C_{16}H_{22}O_6$ (M^+) m/z 310.1417, found 310.1425.

3-(Acetoxymethyl)-6-[(1*E*)-6-formyl-1-hexenyl]-4-methoxy-2*H*-pyran-2-one (34). To a solution of alcohol **33** (10.8 mg, 34.8 μmol) in CH_2Cl_2 (1 mL) was added Dess−Martin periodinane (14.8 mg, 34.8 μmol) with stirring at ambient temperature for 1 h. To this was added additional Dess−Martin periodinane (2.8 mg, 6.6 μmol). The resultant mixture was directly purified by silica gel chromatography ($CHCl_3$/MeOH, 20:1) to give aldehyde **34** (8.9 mg, 83%) as a colorless oil: IR ($CHCl_3$) 1717, 1684 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.44−1.54 (m, 4H), 2.04 (s, 3H), 2.27 (ddt, 2H, J = 1.3, 7.3, 5.9 Hz), 2.47 (dt, 2H, J = 1.3, 7.3 Hz), 3.92 (s, 3H), 4.98 (s, 2H), 6.00 (s, 1H), 6.02 (dt, 1H, J = 15.8, 1.3 Hz), 6.79 (dt, 1H, J = 15.8, 7.3 Hz), 9.77 (t, 1H, J = 1.3 Hz); EI-MS m/z 308 (M^+); EI-HR-MS calcd for $C_{16}H_{20}O_6$ (M^+) m/z 308.1250, found 308.1243.

3-(Acetoxymethyl)-6-[(1*E*,7*E*)-8-iodo-1,7-octadieyl]-4-methoxy-2*H*-pyran-2-one (35). To a suspension of $CrCl_2$-(II) (36.3 mg, 20.3 μmol) in THF (0.03 mL) were added aldehyde **34** (9.1 mg, 29.5 μmol) and iodoform (36.3 mg, 92.1 μmol) in THF (0.07 mL) at 0 °C. The mixture was stirred for 4 h before the reaction was quenched with saturated $NaHCO_3$ and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparative thin layer

silica gel chromatography ($CHCl_3$/EtOAc, 4:1) gave vinyl iodide **35** (7.3 mg, 57%, E/Z = 4:1) and the starting material **34** (4.2 mg, 19%). For **35**: a colorless oil; IR ($CHCl_3$) 1734, 1717 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) (7*E*-isomer) δ 1.40−1.50 (m, 4H), 2.04 (s, 3H), 2.00−2.10 (m, 2H), 2.24 (m, 2H), 3.92 (s, 3H), 4.98 (s, 2H), 5.99 (s, 1H), 5.90−6.00 (m, 1H), 6.49 (dt, 1H, J = 14.5, 7.3 Hz), 6.79 (dt, 1H, J = 15.8, 6.6 Hz); EI-MS *m/z* 432 (M^+); EI-HR-MS calcd for $C_{17}H_{21}O_5I$ (M^+) *m/z* 432.0434, found 432.0466.

3-(Acetoxymethyl)-4-methoxy-6-[(1*E*,7*E*,9*E*)-1,7,9-undecatrienyl]-2*H*-pyran-2-one (36). To bis(acetonitrile)dichloropalladium(II) (0.5 mg, 1.3 μmol) were added 1-(tributylstannyl)propene (16.7 mg, 50.0 μmol) in DMF (0.1 mL) and vinyl iodide **35** (10.9 mg, 25.2 μmol) in DMF (0.1 mL). The mixture was stirred at ambient temperature for 10 min and then filtered through a pad of Celite. The filtrates were diluted with water and extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparative thin-layer silica gel chromatography ($CHCl_3$/ EtOAc, 6:1) gave triene **36** (5.0 mg, 57%) as a colorless oil: IR (NaCl) 1717 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) (7*E*-isomer) δ 1.40−1.50 (m, 4H), 1.73 (d, 3H, J = 6.6 Hz), 2.05 (s, 3H), 2.00−2.10 (m, 2H), 2.24 (m, 2H), 3.92 (s, 3H), 4.99 (s, 2H), 5.40−5.60 (m, 2H), 5.98 (s, 1H), 5.90−6.10 (m, 3H), 6.81 (dt, 1H, J = 15.8, 6.6 Hz); EI-MS *m/z* 346 (M^+); EI-HR-MS calcd for $C_{20}H_{26}O_5$ (M^+) *m/z* 346.1780, found 346.1754.

Prosolanapyrone II (7). To a solution of triene **36** (3.9 mg, 11 μmol) in MeOH (0.5 mL) was added K_2CO_3 (20.0 mg, 0.145 mmol). After 50 min of stirring at ambient temperature, the mixture was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography ($CHCl_3$/EtOAc, 2:1) gave **7** (2.4 mg, 70%) and **36** (0.3 mg, 8%) as a colorless oil.

HPLC Analysis of Nonenzymatic Diels−Alder Reactions of Prosolanapyrones. Prosolanapyrone I (**6**) was diluted with solvents indicated in Table 2 at a concentration of 1 mg/mL. The glass tubes were sealed and heated at indicated temperature over the indicated time (Table 2). Similar experiments for prosolanapyrones II (**7**) and III (**8**) were carried out. An aliquot of each solution was analyzed by HPLC: condition (1) Wakosil-5Sil (ϕ6 × 250 mm, Wako), UV 320 nm, hexane/ EtOAc, 9:1, flow rate 1 mL/min, t_R (min) **1** 9.7, **2** 12.1, **8** 15.2; **3** 13.2, **4** 14.8, **7** 19.5; condition (2) Inertsil ODS-2 (ϕ4.6 × 250 mm, GL science), *i*-PrOH/CH_3CN/H_2O, 3:2:5, flow rate 0.85 mL/min, t_R (min) deoxysolanapyrone (exo) 23.3, (endo) 24.8, **6** 27.5. The values of peak areas were corrected by calibration.

Enzymatic Conversion of Prosolanapyrone II (7). To a 50 mM potassium phosphate buffer (pH 7.0, 15 mL) containing 30% glycerol, the enzyme preparation (5.1 mL) was added. After preincubation at 30 °C for 5 min, a solution of **7** (4.8 mg, 15 μmol) in ethanol (1.5 mL) was added, and the assay mixture was vortexed and then incubated at 30 °C for 2 h. The reaction mixture was passed through a Diaion HP-20 column (3 mL). The column was washed with water, and then adsorbed materials were eluted with EtOAc. The eluent was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel thin-layer chromatography ($CHCl_3$/EtOAc, 2:1) gave **1** (2.4 mg, 51%), **2** (0.48 mg, 10%), and recovered starting material **8** (0.50 mg, 10%). The optical purities of the reaction products were determined as follows. After the concentration of the isolated products was determined from the absorption at 320 nm (ϵ = 7.29 × 10^3, **1**, ϵ = 7.73 × 10^3, **2**), the optical purities were calculated by comparison between the peak areas of the products in the CD spectra and those of enantiomerically pure natural solanapyrones with predefined concentration as follows: (−)-**1** >98% ee, CD λ_{max}/nm (EtOH) 320 ([θ] −7474; natural [θ] −7324); (−)-**2** 67% ee, CD λ_{max}/nm (EtOH) 320 ([θ] −1946; natural −2906).

(±)-Solanapyrone B (3). The sealed tube containing **7** (7.5 mg, 24.5 μmol) in benzene (25 mL) was heated at 140 °C for 24 h. After cooling to ambient temperature, the reaction solution was concentrated in vacuo. Purification by silica gel thin-layer chromatography ($CHCl_3$/EtOAc, 6:1, multiple developments) gave (±)- **3** (1.9 mg, 26%) and (±)-**4** (4.9 mg, 66%) as colorless oils.

Enzymatic Conversion of (−)- and (±)-Solanapyrone B (3). To a 50 mM potassium phosphate buffer (pH 7.0, 0.6 mL) containing 30% glycerol, the enzyme preparation (13.5 μL) was added. After preincubation for 5 min at 30 °C, a solution of (−)-**3** in ethanol (17.4 mM, 0.15 mmol, 8.6 μL) was added to the mixture, and the assay mixture was vortexed and then incubated at 30 °C. At the indicated time (Figure 3), the reaction solution (150 μL) was taken and extracted with EtOAc. To the reaction solutions, 5 μL of 1.25 mM ethyl acetate solution of coumarin was added as an internal standard. An aliquot of the solutions was analyzed by normal phase HPLC [Wakosil-5Sil (ϕ6 × 250 mm, Wako), UV 320 nm, $CHCl_3$/ EtOAc, 2:3, flow rate 1 mL/min, t_R (min) coumarin 6.7, **1** 8.5, **3** 11.8]. Compound (±)-**3** was also incubated, and the reaction products were analyzed in a similar way.

Kinetic Resolution of (±)-Solanapyrone B (3). After removing glycerol with gel filtration column, the enzyme preparation (90 μL) was added to a 50 mM potassium phosphate buffer (pH 7.0, 5 mL). After preincubation for 5 min at 30 °C, (±)-**3** in ethanol (0.31 mg, 1 μmol, 0.24 mL) was added to the mixture and the assay mixture was vortexed and then incubated at 30 °C. After 2 h, the reaction was quenched by addition of EtOAc and vortexed. The organic layer was separated and dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by silica gel thin-layer chromatography ($CHCl_3$/EtOAc, 7:1) gave **1** (0.17 mg, 55%) and **3** (0.06 mg, 18%). After concentrations of the isolated products were determined (ϵ = 2.79 × 10^3, **3** at 320 nm), the optical purity of the reaction products were determined as described: (−)-**1** 27% ee, CD λ_{max}/nm (EtOH) 320 ([θ] −1993); (+)-**3** 91% ee, CD λ_{max}/nm (EtOH) 320 ([θ] +4050; natural −4450)

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Supporting Information Available: ^1H NMR spectra for compounds **6**−**8**, **10**−**12**, **18**, **23a**,**d**, and **29**−**36** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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