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The First Total Synthesis of (−)-Solanapyrone E Based on Domino Michael Strategy

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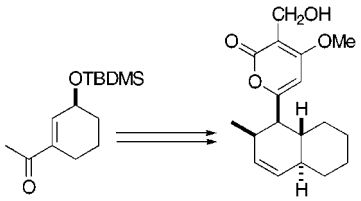
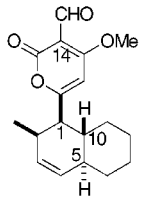
ABSTRACT

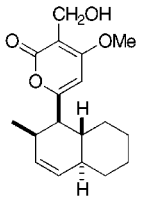


A phytotoxin, solanapyrone E, has been synthesized from the decalone prepared by the domino Michael reaction of the kinetic enolate of optically pure acetylcyclohexene with methyl crotonate. After several transformations on the decalone ring, condensation of a methyl acetoacetate equivalent installed a pyrone moiety and introduction of a hydroxymethyl unit into the pyrone ring furnished solanapyrone E.

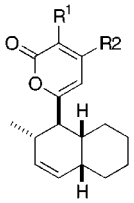
Solanapyrones D (**1**)[1] and E (**2**)[2] are polyketide natural products isolated with solanapyrones A (**3**), B (**4**), or C (**5**)[3] by Oikawa and Ichihara from *Altenaria solani*, a causal fungus of early blight disease to tomato and potato. Phytotoxic activity of these compounds was assayed on growth inhibition of lettuce seedlings,[4] and the formyl derivatives **1** and **3** exhibited complete inhibition at 250 ppm, stronger activity than the hydroxyl analogue **2** and **4**. The structure of solanapyrones contains a characteristic *cis* or *trans* decalin framework and a pyrone moiety with a 14-oxygenated methyl group in common. Racemic solanapyrone A (**3**) has already been synthesized by an intramolecular Diels−Alder reaction as a key step[5] in which solanapyrone D (**1**) was obtained as a byproduct before isolation from the fungus.



Solanapyrone D **1**



Solanapyrone E **2**



Solanapyrone A (R^1=CHO,R^2=OMe) **3**
Solanapyrone B (R^1=CH_2OH,R^2=OMe) **4**
Solanapyrone C (R^1=CHO,R^2=$NHCH_2CH_2OH$) **5**

Investigation of these compounds proved the existence of Diels−Alderase for the first time[2,6] and led to the recent

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(1) Oikawa, H.; Yokota, T.; Ichihara, A.; Sakamura, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1284.
(2) Oikawa, H.; Suzuki, Y.; Naya, A.; Katayama, K.; Ichihara, A. *J. Am. Chem. Soc.* **1994**, *116*, 3605.
(3) Ichihara, A.; Tazaki, H.; Sakamura, S. *Tetrahedron. Lett.* **1986**, *24*, 5373.
(4) Oikawa, H.; Yokota, T.; Sakano, C.; Suzuki, Y.; Naya, A.; Ichihara, A. *Biosci. Biotecnol. Biochem.* **1998**, *62*, 2016.
(5) Ichihara, A.; Miki, M.; Tazaki, H.; Sakamura, S. *Tetrahedron. Lett.* **1987**, *28*, 1175 and earlier references therein.
(6) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748.

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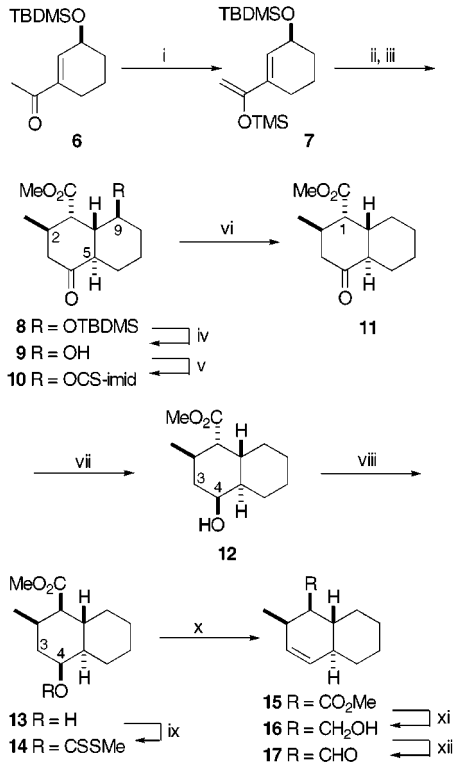
synthesis of the natural solanapyrone A (**3**) by an enzymatic Diels−Alder reaction.[6] These results prompted us to investigate chemical synthesis. We describe herein the first total synthesis of solanapyrone E (**2**) based on our general strategy employing the domino Michael reaction.

The initial part of the synthesis involving stereoselective construction of *trans*-decalone is summarized in Scheme 1.

Scheme 1

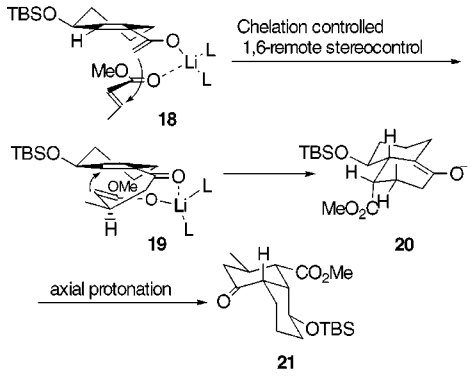


Reagents and conditions: i, LDA (1.2 equiv); TMSCl (1.5 equiv), 93%; ii, MeLi; methyl crotonate (1.1 equiv), HMPA (2 equiv), THF; iii, MeONa (1.3 equiv), MeOH, 86% from **7**; iv, aq. HF, CH_3CN, 94%; v, 1,1′-thiocarbonyldiimidazole (1.5 equiv), 90%; vi, AIBN, Bu_3SnH (1.6 equiv), benzene, 94%; vii, L-Selectride (1.5 equiv), aq. NaOH, H_2O_2, THF, 90%; viii, *t*-BuOK (1 equiv), *t*-BuOH, DMSO, 78%; ix, *t*-BuOK (2.5 equiv); CS_2, MeI, THF, 91%; x, 1-methylnaphthalene, 190 °C; xi, LAH (3 equiv), Et_2O, 89% from **14**; xii, PCC (3 equiv), 4Å-MS, CH_2Cl_2.

The synthesis started from enantiomerically pure trimethylsilylenol ether **7** of (*S*)-acetylcyclohexene **6** obtained by lipase-catalyzed enantioselective acylation.[7,8] As previously exemplified in the successful total synthesis of (+)-compactin,[8] domino Michael reaction between methyl crotonate and the kinetic enolate of **6** provided stereoselectively a decalone which was subsequently treated with base to ensure isomerization into more stable *trans*-decalone **8** in 86% overall yield. It is important in the presence of 2 equiv of hexamethylphosphortriamide (HMPA) to employ the kinetic enolate of **6** generated by cleavage of the trimethylsilylenol ether **7** by methyllithium. Rigorous NMR study of the decalone **8** revealed that the ester group at C-1 still remained in an α-axial position. The proton at C-1 appeared at δ 3.02 (t-like, J 2.1 Hz) and had a W-type long-range coupling with the β-equatorial proton at C-3.

From the relative stereochemistry of the decalone **8**, the present domino Michael reaction is anticipated to proceed according to the pathway shown in Scheme 2. The first

Scheme 2



Michael addition occurred from the less hindered α-face of the enolate to *s-cis*-crotonate which was connected by chelation to the enolate. The second Michael addition occurred from the same face, keeping chelation, to give enolate **20**. Axial protonation to the enolate **20** furnished the decalone **21** having a *cis*-steroidal conformation. After the usual aqueous workup procedure, an inseparable mixture of the decalones **8** and **21** was isolated. It is worth noting that the chiral center in **7** controls the stereochemistry of the first Michael reaction and consequently subsequent reactions.

The chiral directing siloxy group at C-9 in the decalone **8** was removed prior to introduction of double bond at C-3. Deprotection of the TBDMS group with aqueous hydrogen fluoride (HF) gave alcohol **9**[9] in 94% yield, and subsequent solid-state reaction with thiocarbonyldiimidazole[10] successfully provided thiocarbonylimidazolide **10** in 90% yield. The reaction proceeded simply by grinding the substrate **9** and thiocarbonyldimidazole with a pestle in a mortar under a nitrogen atmosphere. Probably due to the proximity of the hydroxy group at C-9 with the ester group at C-1, all conventional attempts to prepare xanthate via alkoxide failed. The imidazolide **10** was reduced with *n*-tributyltin hydride in hot benzene to afford decalone **11** in 94% yield. To introduce a double bond selectively at C-3 by *syn* elimination, the carbonyl group at C-4 of the decalone **11** was reduced with L-Selectride to give axial alcohol **12** in 90% yield.

(7) Hagiwara, H.; Nakano, T.; Uda, H. *Bull. Chem. Soc. Jpn*. **1993**, *66*, 3110.

(8) Hagiwara, H.; Kon-no, M.; Nakano, T.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 777.

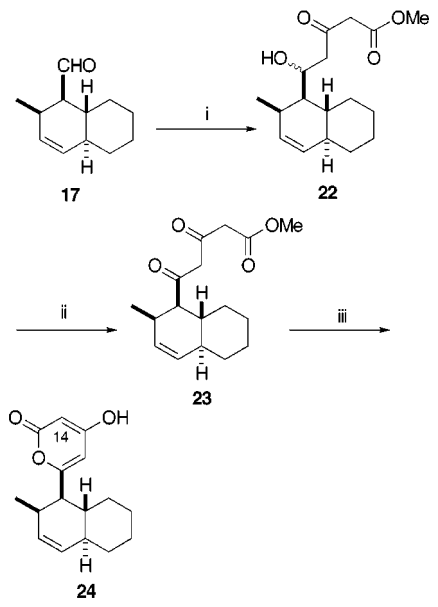
(9) All new compounds from **9** to **14** and **16** gave satisfactory combustion analyses. Compounds **15** and **17** were used for further transformation without purification. Compounds **22**−**27** were transformed soon after purification.

(10) Hagiwara, H.; Ohtsubo, S.; Kato, M. *Tetrahedron* **1997**, *53*, 2415.

According to MM2 calculations[11] of all plausible substrates for the isomerization at C-1, the energy stabilization of the decalone **12** was the largest after isomerization into **13**. To this end, the α-axial ester group of **12** was then isomerized into the thermodynamically more stable *β*-equatorial orientation by treatment with potassium *tert*-butoxide (*t*-BuOK) in dimethyl sulfoxide (DMSO) to furnish decalone **13** having all the requisite stereocenters for solanapyrones D (**1**) and E (**2**). Alcohol **13** was transformed into xanthate **14** in 91% yield using *t*-BuOK as a base. Then a double bond was selectively introduced at C-3 by xanthate pyrolysis. After heating the xanthate **14** in 1-methylnaphthalene at 190 °C, to the resulting solution of ester **15** was directly added lithium aluminum hydride (LAH) to give alcohol **16** in 89% overall yield over two steps. Pyridinium chlorochromate (PCC) oxidation of alcohol **16** provided aldehyde **17** which was used for the next transformation without further purification.

Installation of the pyrone ring is summarized in Scheme 3. Aldehyde **17** was reacted with the bistrimethylsilyl enol

Scheme 3

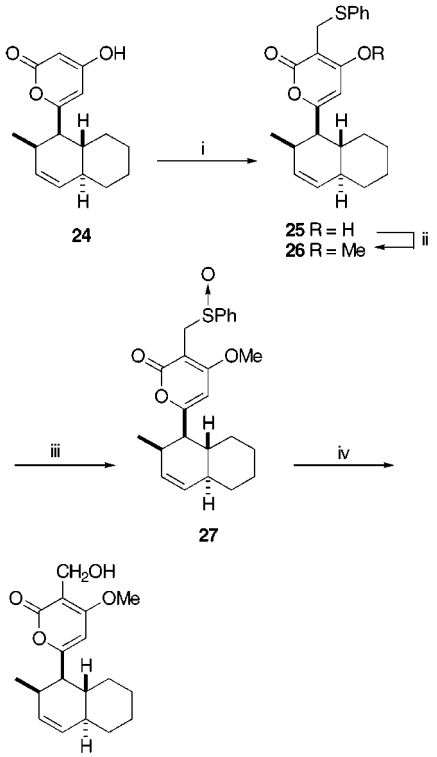


Reagents and conditions: i, methyl acetoacetate bisTMS enol ether (5 equiv), $TiCl_4$ (1 equiv), CH_2Cl_2, 73% from **16**; ii, Jones reagent, acetone, 74%; iii, DBU (2 equiv), benzene, 93%.

ether of methyl acetoacetate[12] in the presence of titanium tetrachloride ($TiCl_4$) to afford *δ*-hydroxy-*β*-ketoester **22** in 73% yield from alcohol **16**. Jones oxidation provided *β*,*δ*-diketoester **23** in 74% yield, and subsequent treatment with DBU[13] furnished pyrone **24** in 93% yield.

Introduction of the hydroxymethyl group at C-14 was not a trivial task. Model experiments of 4-hydroxypyrone with formaldehyde provided dimeric compounds. Nucleophilicity of the vinylic carbanion at C-2 of 4-methoxypyrone was low. However, we found our original method which is summarized in Scheme 4. The phenylthiomethyl group was

Scheme 4



Reagents and conditions: i, $(HCHO)_n$, PhSH, AcOH, piperidine, EtOH, 84%; ii, Me_2SO_4 (5 equiv), K_2CO_3, acetone, 77%; iii, MCPBA (1 equiv), CH_2Cl_2, 88%; iv, $(CF_3CO)_2O$ (4 equiv), CH_2Cl_2; aq. NaOH, THF, 62%.

introduced to pyrone **24** with paraformaldehyde and thiophenol (PhSH) according to the procedure of Moreno-Manas et al.[14] to give sulfide **25** in 84% yield. Conventional *O*-methylation of sulfide **25** provided in 77% yield methyl ether **26** which was oxidized with MCPBA to give sulfoxide **27** in 88% yield. Final treatment of sulfoxide **27** with trifluoroacetic anhydride followed by basic workup completed the total synthesis of solanapyrone E (**2**) in 62% yield. The reaction is explained as methoxy group assisted substitution of trifluoroacetoxysulfonium ion by trifluoroacetoxy anion. No aldehydic product as a result of Pummerer reaction was isolated. Detailed results on the introduction of a hydroxy-

(11) Molecular modeling was performed using PCMODEL (Serena Software, Bloomington, IN).

(12) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 693.

(13) Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron. Lett.* **1996**, *37*, 2997.

(14) (a) de March, P.; Moreno-Manas, M.; Pi, R.; Trius, A. *J. Heterocycl. Chem.* **1982**, *19*, 335. (b) Moreno-Manas, M. *Synthesis* **1984**, 430.

(15) The optical rotation of stable synthetic intermediates in $CHCl_3$ at 20 °C were as follows: **8** $[\alpha]_D$ +43.1 (*c* 1.01), **9** $[\alpha]_D$ +43.8 (*c* 1.00), **10** $[\alpha]_D$ +20.3 (*c* 1.00), **11** $[\alpha]_D$ +27.1 (*c* 1.00), **12** $[\alpha]_D$ +39.5 (*c* 1.00), **13** $[\alpha]_D$ −31.2 (*c* 1.00), **14** $[\alpha]_D$ −29.9 (*c* 1.10), **16** $[\alpha]_D$ −126.8 (*c* 1.07), and **26** $[\alpha]_D$ −121.7 (*c* 0.98).

methyl unit to the pyrone ring will be reported in due course. NMR data (500 MHz) of synthetic solanapyrone E (**2**) were completely identical with those of the natural product kindly provided by Prof. Oikawa {$[\alpha]_D$ −155° ($CHCl_3$, *c* 0.93), lit.[4] $[\alpha]_D$ −76° ($CHCl_3$, *c* 1.0)}.[15]

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Supporting Information Available: NMR spectra (500 MHz) of both synthetic and natural compounds **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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