Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 6296–6305
Tetrahedron

# Synthetic studies toward plakortide E: application of the Feldman oxygenation to synthesis of highly substituted 1,2-dioxolanes

Qiong Zhao[a] and Henry N. C. Wong[a,b,c,d,*]

[a]*Shanghai–Hong Kong Joint Laboratory in Chemical Synthesis, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, 354 Feng Lin Road, Shanghai, China*
[b]*Department of Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China*
[c]*Center of Novel Functional Molecules, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China*
[d]*Institute of Chinese Medicine, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong, China*

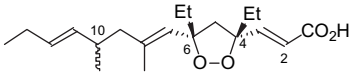
Received 21 January 2007; revised 24 February 2007; accepted 27 February 2007
Available online 2 March 2007

**Abstract**—The Feldman radical oxygenation of vinylcyclopropanes is successfully applied to the synthesis of the highly substituted core of the 1,2-dioxolane natural product, plakortide E. The ratio of the desired *cis*-1,2-dioxolane can be enhanced by choice of cyclopropane substituents.


## 1. Introduction

The chemistry of five-membered peroxides (1,2-dioxolanes) has been rejuvenated in the last decades because some of the naturally occurring five-membered peroxides isolated from terrestrial or marine sources (such as the marine sponges *Plakortis* sp.) exhibit remarkable bioactivities including antimalarial, antifungal, antiviral, and cytotoxic properties.[1]

We have been interested in the synthesis of molecules isolated from the Jamaican marine sponge *Plakortis halichondrioides* of which plakortide E (**1**) is one of our targets. Plakortide E presents challenging issues due to its unknown absolute configuration, lack of stereochemical assignment for C10, and the presence of the two tertiary peroxide centers in the 1,2-dioxolane.[1a]



**plakortide E (1)**

Although many methods have been developed in the past to construct the peroxide ring, most of them demand low temperature operations and mild conditions, and the yields are less than satisfactory because such products contain a weak O–O bond.[2] Recently, significant progress has been made in the synthesis of five-membered cyclic peroxides. Bloodworth and co-workers prepared four non-natural five-membered ring plakinic acids in racemic form via sequential peroxymercuration and in situ reduction with sodium borohydride.[3] A recent article disclosed that Lewis acid-mediated annulation reactions of alkenes with peroxycarbenium ions enable the preparation of 1,2-dioxolanes, and triethylsilyl-protected peroxycarbenium ions are most suitable for these reactions.[4] Based on the elegant synthetic routes developed in his laboratory,[5] Dussault achieved for the first time the asymmetric synthesis and configurational assignment of plakinic acid A in 2006.[5h] A regio- and stereoselective opening of an enantiomerically enriched oxetane by hydrogen peroxide led to a hydroperoxyalcohol, which was elaborated into the 1,2-dioxolanic product (Scheme 1).

However, despite these and other approaches for the synthesis of five-membered ring peroxides, no synthesis has been reported for any member of the plakortide family, which features tertiary, allylic, peroxide subunits. In this paper, we describe the first synthesis of a *cis*-1,2-dioxolane containing suitable substitution and functionality for elaboration to plakortide E.

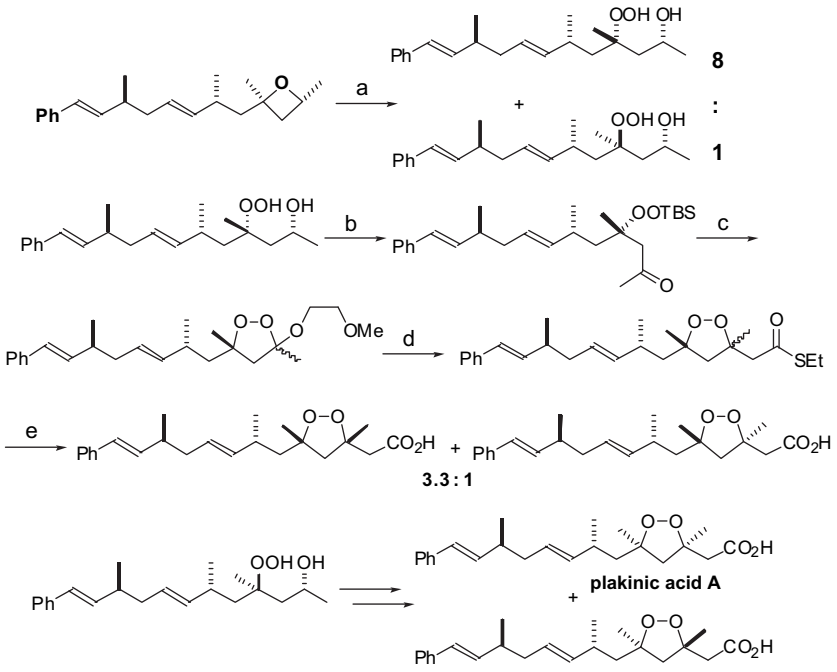
## 2. Results and discussion

The salient feature in our strategy is a radical [3+2] oxygenation of highly substituted vinylcyclopropanes, a reaction that introduces two tertiary peroxide linkages in a single step.[6] The retrosynthetic pathway is depicted in Figure 1.

The key intermediate diethyl 1,2-diethyl-1,2-cyclopropanedicarboxylate (**5**) was prepared by the McCoy procedure

*Keywords*: Peroxide; Plakortide E; Feldman reaction; Radical; Five-membered ring.
* Corresponding author. Tel.: +852 2609 6329; fax: +852 2603 5057; e-mail: hncwong@cuhk.edu.hk

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.02.121




**Scheme 1**. Reagents and conditions: (a) $Me_3SiOTf$, $H_2O_2$, $Et_2O$, −78 °C, 57%; (b) $LiN(SiMe_3)_2$, *t*-$BuMe_2SiCl$, Dess–Martin periodinane, 80%; (c) HF, $MeOCH_2CH_2OH$, two days, 88%; (d) $TiCl_4$, $H_2C{=}C(OSiMe_3)SEt$, −50 to 0 °C, 88%; (e) NaOMe, MeOH, LiOH, $H_2O_2$, THF, 92%.

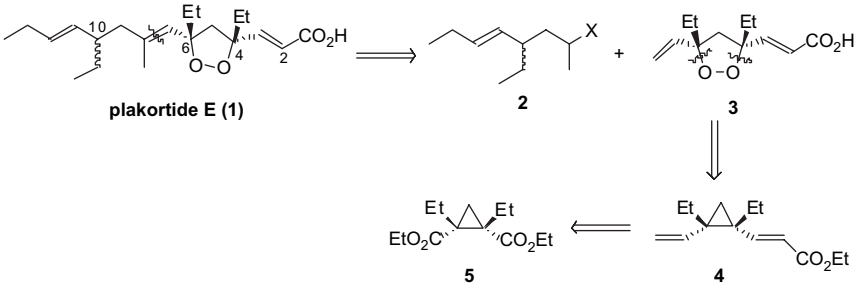
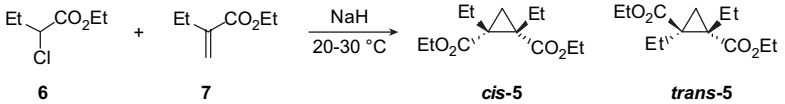



**Figure 1**. Retrosynthetic analysis for plakortide E.

starting from ethyl α-chlorobutyrate (**6**) and ethyl α-ethylacrylate (**7**).[7] In the cyclopropanation, solvent exerts marked effect on the isomer ratio, so we were able to synthesize either of the two isomers in a stereoselective manner by changing the solvent (Scheme 2).

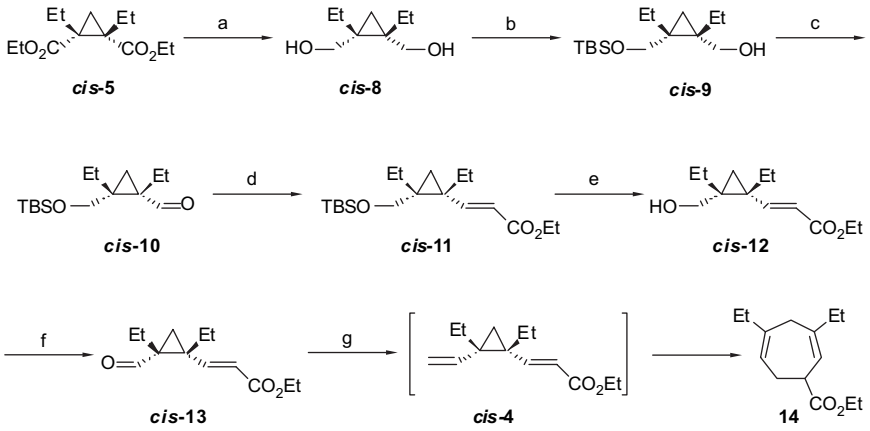
Because of the cis configuration of plakortide E, our synthesis began with diethyl *cis*-1,2-diethyl-1,2-cyclopropanedicarboxylate (*cis*-**5**). After reduction with $LiAlH_4$, we obtained diol *cis*-**8**,[8] which was monoprotected with *t*-$BuMe_2SiCl$.[8] Swern oxidation of *cis*-**9** generated *cis*-**10**,[9] and the subsequent Horner–Emmons reaction with triethyl phosphonoacetate led to the unsaturated ester *cis*-**11**.[10] Deprotection of *cis*-**11** with 3 M HCl afforded *cis*-**12**,[11] which was again submitted to Swern oxidation to give *cis*-**13**. The expected product of olefination, *cis*-**4** was not isolated but instead underwent rapid Cope rearrangement to furnish cycloheptadiene **14** (Scheme 3).

We therefore changed our strategy to focus on a *trans*-divinyl cyclopropane as a precursor for the radical oxygenation. *trans*-**13**, available from *trans*-**5** (49%, six steps), underwent

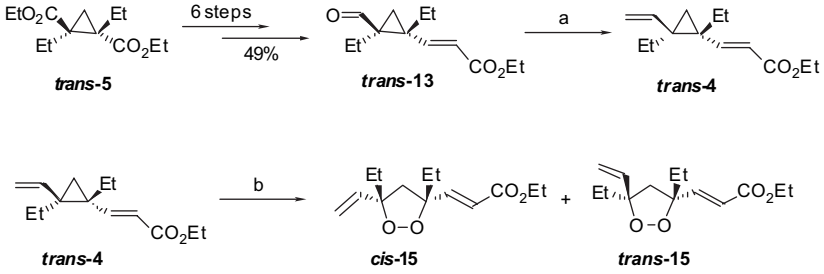



| solvent | toluene | benzene/HMPA |
|---|---|---|
| *cis*/*trans* | 100/0 | 1/2.5 |
| yield(%) | 82 | 80 |

**Scheme 2**.




**Scheme 3**. Reagents and conditions: (a) $LiAlH_4$, $Et_2O$, 0 °C to reflux, 87%; (b) TBSCl, $Et_3N$, $CH_2Cl_2$, 0 °C, 78%; (c) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 81%; (d) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF, rt, 72%; (e) 3 M HCl, THF, 0 °C to rt, 95%; (f) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C, 81%; (g) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, 0 °C, 14%.




**Scheme 4**. Reagents and conditions: (a) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, −78 °C, 76%; (b) $Ph_2Se_2$, AIBN, $O_2$, MeCN, 0 °C, 88%.

olefination to furnish *trans*-**4**.[10b] Irradiation with a 300 W sunlamp at 0 °C under an atmosphere of $O_2$ and in the presence of catalytic amounts of $Ph_2Se_2$ and AIBN furnished 1,2-dioxolane **15** in 88% yield (Scheme 4)[6] and as a 1/7 mixture of diastereomers ($^1$H, HPLC). The trans configuration of the major diastereomer was established by NOE studies (Fig. 2).

Thus the Feldman protocol entirely suits our purpose as we have realized the construction of 1,2-dioxolanes with both oxygen atoms linking to tertiary carbon centers. While both experimental[6a–d] and computational results[6e] support the notion that the cis-products should predominate in the [3+2] radical addition, however, the major products from the peroxidation of compound **4** have a trans configuration. We sought to increase the proportion of cis-product, which was desired as a precursor for plakortide E.

In the accepted mechanism for the peroxidation (Fig. 3),[6c] the dioxolane stereochemistry is set during ring closure of substituted 5-hexenylperoxy radical. The stereochemical outcome of this transformation depends primarily upon the nature of the substituents.[6e]

To clarify the situation, we prepared a series of vinylcyclopropanes and subjected them to the peroxidation. A *trans*-2-vinylcyclopropane carboxylic acid (*trans*-**18**), prepared in three steps from *trans*-**10** (Scheme 5), was converted to an amide (*trans*-**19**),[12] esters *trans*-**20**[13] and *trans*-**21**[14] (Scheme 6). In all three substrates, the acyl group is considered a radical-stabilizing substituent.

The peroxidation results are summarized in Table 1. As for **23** and **25**, the peroxidation at 30–40 °C for two days

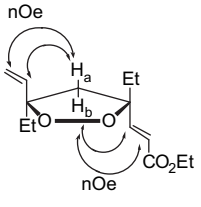



**Figure 2**. NOESY results of *trans*-**15**.

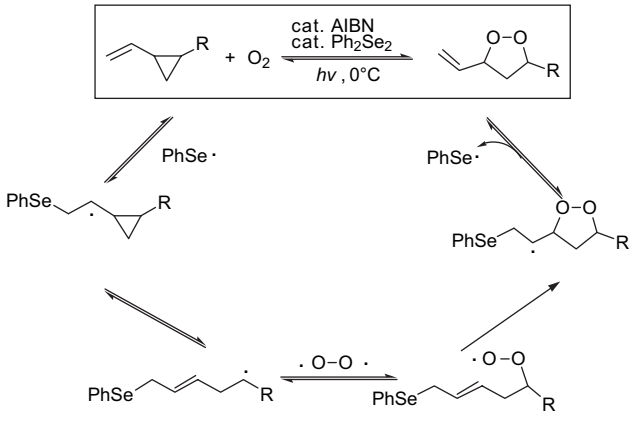
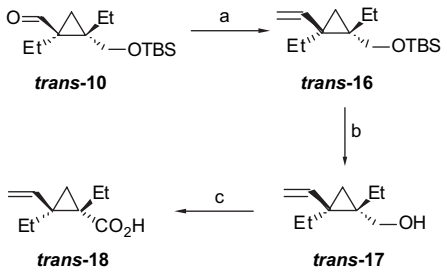
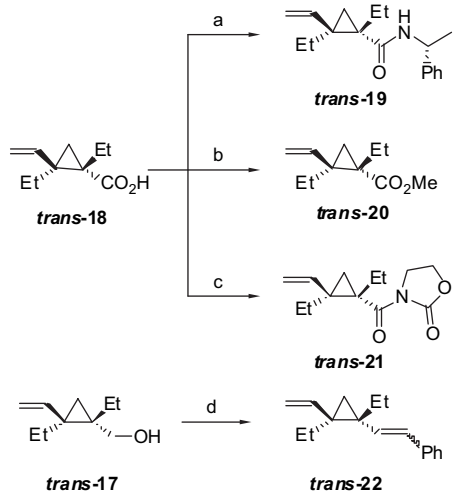



**Figure 3**.




**Scheme 5**. Reagents and conditions: (a) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, 0 °C to rt, 95%; (b) *p*-TsOH, MeOH/$CH_2Cl_2$, 94%; (c) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C; $NaClO_2$, $KHPO_4$, resorcinol, *t*-BuOH/$H_2O$, 70%.

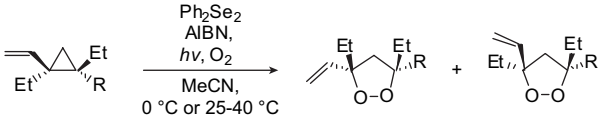
furnished very high yields of 1,2-dioxolanes. To our disappointment, the cis/trans ratios are lower than for the original oxygenation to furnish **15**, in fact, amide **19** reacted to only furnish *trans*-**23** in which the diastereoisomer ratio is 1/1. These products were isolated and purified by standard methods, with cis/trans ratios determined by $^1H$ NMR and HPLC methods. The trans configurations of the major diastereomers were all established by NOE studies. Peroxides **23**, **24**, and **25** are as stable as **15** upon prolonged storage at room temperature.




**Scheme 6**. Reagents and conditions: (a) $(COCl)_2$, $CH_2Cl_2$, (*R*)-1-methylbenzyl amine, $Et_3N$, $CH_2Cl_2$, rt, 65%; (b) $CH_2N_2$, $Et_2O$, 0 °C, 94%; (c) $(COCl)_2$, $CH_2Cl_2$, oxazolidin-2-one, *n*-BuLi, THF, −78 °C, 75%; (d) $(COCl)_2$, DMSO, $CH_2Cl_2$, −78 °C; $Ph_3P^+CH_2PhBr^-$, *n*-BuLi, THF, 0 °C to rt, 71%.

The Feldman group performed a utilized ab initio computation at the MP2/6-31G*//UHF/6-31G* level to gain an

**Table 1**




| Substrate | Products | | Yield (%) | cis/trans |
|---|---|---|---|---|
| *trans*-**4** | *cis*-**15** | *trans*-**15** | 88 | 1/7 |
| *trans*-**19** | *cis*-**23a** + *cis*-**23b** | *trans*-**23a** + *trans*-**23b** | quant | trans |
| *trans*-**20** | *cis*-**24** | *trans*-**24** | 75 | 1/22 |
| *trans*-**21** | *cis*-**25** | *trans*-**25** | quant | 1/13 |
| *trans*-**22** | *cis*-**26** | *trans*-**26** | 82 | 1/2.8 |

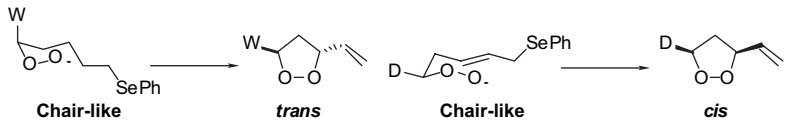
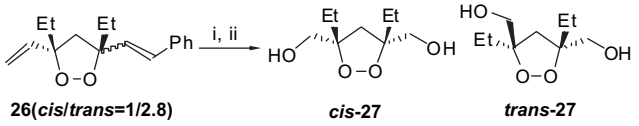



**Figure 4**.




**Scheme 7**. Reagents and conditions: (i) $O_3$, $CH_2Cl_2$, −78 °C; (ii) $NaBH_4$, −78 °C to rt, 80%.

understanding of structural correlation for the cis/trans ratio of the products.[6e] Their results indicate that in a favorable chair-like transition state, an electron-withdrawing group would prefer an axial disposition that leads to a trans-product. On the other hand, electron-donating group will occupy an equatorial position to give a cis-product (Fig. 4).

Accordingly, we investigated oxygenation of *trans*-**22**,[15] which contains an electron-rich styrenyl substituent (Scheme 7). Radical oxygenation under similar conditions as above furnished the 1,2-dioxolane **26** as an inseparable 1/2.8 mixture of cis/trans isomers. This was the best result among the five substrates tested (Table 1). This result might suggest that the aryl group plays an important role in the stereocontrol process, possibly by π–π stacking with the phenylseleno group in the radical intermediate (Fig. 5).

The mixture was subjected to ozonolysis, which on reductive workup with $NaBH_4$ gave two chromatographically separable diols **27** (Scheme 7). The *cis*-**27** is the key synthetic precursor for plakortide E, which would be used in the following linkage of the side chain and the peroxide ring.

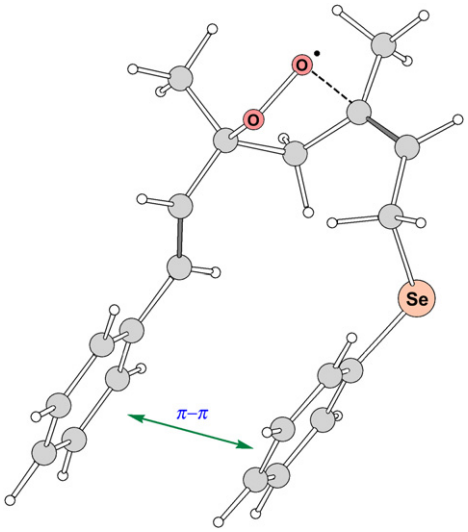



**Figure 5**. Peroxy radical intermediate from *trans*-**22** optimized with UMPWB1K/6-31G* method (not complete).

## 3. Conclusion

We have successfully synthesized the five-membered cyclic peroxide fragment of plakortide E via a radical oxygenation of cyclopropanes. By modification of the cyclopropane substituents, we improved the cis/trans ratio from 1/7 to 1/2.8, and obtained the key synthetic precursor *cis*-**27** from *trans*-**5** in eight steps with a 7% overall yield. Further linkage of the side chain with the *cis*-peroxide and the total synthesis of plakortide E are under investigation.

## 4. Experimental

### 4.1. General

$^1$H NMR spectra were recorded on a Bruker AM-300 (300 MHz) or on a Varian Mercury 300 (300 MHz) spectrometer. $^{13}$C NMR spectra were recorded on a Bruker DPX-400 (100.4 MHz) or on a Varian Mercury 300 (75.3 MHz) spectrometer, in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet. Infrared (IR) spectra were measured on a Bio-Rad FTS-185 spectrophotometer. Elemental analyses were performed in an Elemantar Vario EL apparatus. High-resolution mass spectra (MS) were measured on a Kratos Concept 1H or on a Bruker Daltonics FTMS-7 instrument. Solvents were dried and purified according to standard procedures. Column chromatography was carried out with Qingdao Haiyang silica gel (300–400 mesh).

**4.1.1. Diethyl *cis*-1,2-diethylcyclopropane-1,2-dicarboxylate (*cis*-5).** A stirred suspension of sodium hydride (60% suspension in mineral oil, 2.5 g, 63 mmol) in dry toluene (10 mL) was treated under nitrogen with ethyl 2-chlorobutyrate (7.5 g, 50 mmol) and ethyl 2-ethylacrylate (6.4 g, 50 mmol). The reaction temperature was maintained between 20 and 40 °C. After the addition, the reaction was monitored with TLC. At the end, residual sodium hydride was destroyed by addition of a small amount of methanol. Sufficient water (15 mL) was added to dissolve the sodium halide, and the mixture was extracted with $Et_2O$ (20 mL×3), washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated. The residual oil was distilled under reduced pressure to give *cis*-**5** as a colorless oil (9.9 g, 82%); bp: 130 °C/10 torr; $^1$H NMR: $\delta$ 4.07–4.14 (q, 4H, $J$=7.5 Hz), 1.95–2.02 (m, 2H, $J$=7.5 Hz), 1.87 (d, 1H, $J$=4.5 Hz), 1.43–1.50 (m, 2H, $J$=7.5 Hz), 1.24 (t, 6H, $J$=7.5 Hz), 1.01 (t, 6H, $J$=7.5 Hz), 0.66 (d, 1H, $J$=4.5 Hz); $^{13}$C NMR: $\delta$ 180.9, 66.1, 32.8, 29.8, 23.8, 21.2, 11.6; IR (film, cm$^{-1}$): 1726, 1380, 1328, 1246, 1189, 1149; $m/z$ 242 ($M^+$); HRMS $C_{13}H_{22}O_4$ ($M^+$) required 242.1518, found 242.1516.

**4.1.2. Diethyl *trans*-1,2-diethylcyclopropane-1,2-dicarboxylate (*trans*-5).** To a suspension of sodium hydride

(60% suspension in mineral oil, 12.2 g, 0.3 mol) in dry HMPA (130 mL) under nitrogen was added a solution of **6** (38.7 g, 0.26 mmol) and **7** (33.6 g, 0.26 mmol) in benzene (130 mL) dropwise. The reaction temperature was maintained between 20 and 40 °C. At the end of the reaction, a small amount of methanol was added, which was followed by water (650 mL). The mixture was extracted with $Et_2O$ (650 mL×1, 400 mL×2), and the combined organic extracts were washed with water (1000 mL) and brine (1000 mL), dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by flash chromatography (hexane/EtOAc, 20/1) to give firstly *trans*-**5** (36 g, 57%) followed by *cis*-**5** (14.5 g, 23%); $^1$H NMR: $\delta$ 4.13–4.25 (m, 4H, $J$=7.5 Hz), 1.98–2.14 (m, 2H, $J$=7.5 Hz), 1.33 (s, 2H), 1.28 (t, 6H, $J$=7.5 Hz), 1.07–1.20 (m, 2H, $J$=7.5 Hz), 0.93 (t, 6H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 171.4, 60.7, 37.7, 23.3, 19.9, 14.1, 11.4; IR (film, cm$^{-1}$): 1729, 1458, 1234, 1182; *m*/*z* 242 ($M^+$); HRMS $C_{13}H_{22}O_4$ ($M^+$) required 242.1518, found 242.1513.

**4.1.3. *cis*-1,2-Diethyl-1,2-bis(hydroxymethyl)cyclopropane (*cis*-8).** To a stirred suspension of lithium aluminum hydride (2.8 g, 74 mmol) in $Et_2O$ (70 mL) at 0 °C was added a solution of *cis*-**5** (8.6 g, 35.5 mmol) in $Et_2O$ (30 mL). Upon complete disappearance of *cis*-**5**, the reaction mixture was quenched with water (2.8 mL), then 15% sodium hydroxide (2.8 mL), and finally water (8.4 mL). The mixture was filtered through Florisil and the filter cake was washed with $Et_2O$ (20 mL×3). The filtrate was dried over $MgSO_4$ and evaporated by rotary evaporation. Further purification by flash chromatography (hexane/EtOAc, 4/1) gave *cis*-**8** as a colorless viscous oil (4.88 g, 87%); $^1$H NMR: $\delta$ 4.02 (d, 2H, $J$=12.0 Hz), 3.36 (d, 2H, $J$=12.0 Hz), 2.90 (s, 2H), 1.75–1.90 (m, 2H, $J$=7.5 Hz), 1.23–1.41 (m, 2H, $J$=7.5 Hz), 1.01 (t, 6H, $J$=7.5 Hz), 0.33 (d, 1H, $J$=4.8 Hz), 0.24 (d, 1H, $J$=4.8 Hz); $^{13}$C NMR: $\delta$ 66.0, 32.5, 23.6, 21.0, 11.6; IR (film, cm$^{-1}$): 3338 (br s, OH), 1467, 1207; HRMS $C_9H_{18}O_2Na$ ($M^+$+Na) required 181.1199, found 181.1198.

**4.1.4. *trans*-1,2-Diethyl-1,2-bis(hydroxymethyl)cyclopropane (*trans*-8).** It was prepared in the same manner as *cis*-**8** in 88% yield; $^1$H NMR: $\delta$ 3.8 (d, 2H, $J$=11.4 Hz), 3.42 (d, 2H, $J$=11.4 Hz), 2.44 (s, 2H), 1.74–1.89 (m, 2H, $J$=7.5 Hz), 1.35–1.50 (m, 2H, $J$=7.5 Hz), 0.98 (t, 6H, $J$=7.5 Hz), 0.28 (s, 2H); $^{13}$C NMR: $\delta$ 63.2, 32.8, 21.7, 19.0, 11.0; IR (film, cm$^{-1}$): 3333 (br s, OH), 1467, 1027; HRMS $C_9H_{18}O_2Na$ ($M^+$+Na) required 181.1199, found 181.1195.

**4.1.5. *cis*-1,2-Diethyl-2-(hydroxymethyl)-[(*tert*-butyldimethylsiloxy)methyl]cyclopropane (*cis*-9).** To a solution of *cis*-**8** (275 mg, 1.74 mmol) and triethylamine (0.5 mL, 3.6 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (263 mg, 1.74 mmol) in $CH_2Cl_2$ (2 mL). After 2 h at 0 °C, a white precipitate formed. The reaction mixture was washed with water (5 mL), dried over $Na_2SO_4$, filtered, and concentrated to give a yellow oil, which was purified by flash chromatography (hexane/EtOAc, 40/1) to give *cis*-**9** as a colorless oil (0.37 g, 78%); $^1$H NMR: $\delta$ 4.04 (d, 1H, $J$=11.4 Hz), 3.87 (d, 1H, $J$=12.0 Hz), 3.36 (d, 1H, $J$=11.4 Hz), 3.33 (d, 1H, $J$=12.0 Hz), 1.8–1.95 (m, 1H, $J$=7.5 Hz), 1.68–1.8 (m, 1H, $J$=7.5 Hz), 1.2–1.40 (m, 2H, $J$=7.5 Hz), 1.01 (t, 3H, $J$=7.5 Hz), 0.97 (t, 3H, $J$=7.5 Hz), 0.91 (s, 9H), 0.30 (d, 1H, $J$=4.8 Hz), 0.21 (d, 1H, $J$=4.8 Hz), 0.11 (s, 3H), 0.10 (s, 3H); $^{13}$C NMR: $\delta$ 66.9, 66.2, 33.6, 32.4, 25.9, 24.0, 23.8, 20.9, 20.8, 18.2, 11.7, 11.7; IR (film, cm$^{-1}$): 3497, 1471, 1256, 1053, 838; *m*/*z* 272 ($M^+$). Anal. Calcd for $C_{15}H_{32}O_2Si$: C 66.11, H 11.84. Found: C 66.15, H 11.93.

**4.1.6. *trans*-1,2-Diethyl-2-(hydroxymethyl)-[(*tert*-butyldimethylsiloxy)methyl]cyclopropane (*trans*-9).** It was prepared in the same manner as *cis*-**9** in 82% yield; $^1$H NMR: $\delta$ 3.72 (d, 1H, $J$=10.8 Hz), 3.67 (d, 1H, $J$=10.5 Hz), 3.54 (d, 1H, $J$=10.5 Hz), 3.41 (d, 1H, $J$=10.8 Hz), 1.40–1.72 (m, 4H, $J$=7.5 Hz), 0.98 (t, 3H, $J$=7.5 Hz), 0.94 (t, 3H, $J$=7.5 Hz), 0.89 (s, 9H), 0.30 (d, 1H, $J$=4.8 Hz), 0.28 (d, 1H, $J$=4.8 Hz), 0.04 (s, 3H), 0.04 (s, 3H); IR (film, cm$^{-1}$): 3364 (br s, OH), 1473, 1256, 1077. Anal. Calcd for $C_{15}H_{32}O_2Si$: C 66.11, H 11.84. Found: C 66.00, H 11.95.

**4.1.7. *cis*-1,2-Diethyl-2-[(*tert*-butyldimethylsiloxyl)-methyl]cyclopropanecarboxaldehyde (*cis*-10).** A solution of DMSO (0.13 mL, 1.85 mmol) in $CH_2Cl_2$ (2 mL) was added to a solution of oxalyl chloride (0.07 mL, 0.74 mmol) in $CH_2Cl_2$ (2 mL) at −78 °C over 30 min, followed by a solution of *cis*-**9** (200 mg, 0.74 mmol) in $CH_2Cl_2$ (2 mL). The resulting mixture was stirred at the same temperature for 30 min, and then $Et_3N$ (0.5 mL, 3.7 mmol) was added. After another 20 min, water (10 mL) and $CH_2Cl_2$ (10 mL) were added, and the whole was partitioned. The aqueous layer was extracted with $CH_2Cl_2$ (20 mL×3). The combined organic layers were successively washed with 1% HCl (30 mL), $H_2O$ (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL), and dried over $Na_2SO_4$. After removal of the solvents, the crude product was purified by column chromatography (hexane/EtOAc, 40/1) to give *cis*-**10** as a colorless oil (0.16 g, 81%); $^1$H NMR: $\delta$ 9.33 (s, 1H), 3.86 (d, 1H, $J$=11.2 Hz), 3.42 (d, 1H, $J$=11.2 Hz), 1.55–1.91 (m, 4H), 1.42 (d, 1H, $J$=4.8 Hz), 0.98 (t, 3H, $J$=7.5 Hz), 0.96 (t, 3H, $J$=7.5 Hz), 0.84 (s, 9H), 0.70 (d, 1H, $J$=4.8 Hz), 0.01 (s, 3H), 0.01 (s, 3H); IR (film, cm$^{-1}$): 1711 (C═O), 1257, 1087, 838. Anal. Calcd for $C_{15}H_{30}O_2Si$: C 66.61, H 11.18. Found: C 67.04, H 11.06; HRMS $C_{15}H_{31}O_2Si$ ($M^+$+H) required 271.2088, found 271.2101.

**4.1.8. *trans*-1,2-Diethyl-2-[(*tert*-butyldimethylsiloxyl)-methyl]cyclopropanecarboxaldehyde (*trans*-10).** It was prepared in the same manner as *cis*-**10** in 87% yield; $^1$H NMR: $\delta$ 9.30 (s, 1H), 3.69 (d, 1H, $J$=11.2 Hz), 3.60 (d, 1H, $J$=11.2 Hz), 1.76–1.91 (m, 2H), 1.47–1.74 (m, 2H), 1.35 (d, 1H, $J$=4.8 Hz), 0.96 (t, 3H, $J$=7.5 Hz), 0.93 (t, 3H, $J$=7.5 Hz), 0.90 (s, 9H), 0.87 (d, 1H, $J$=4.8 Hz), 0.06 (s, 3H), 0.06 (s, 3H); IR (film, cm$^{-1}$): 1708 (C═O); *m*/*z* 270 ($M^+$); HRMS $C_{15}H_{31}O_2Si$ ($M^+$+H) required 271.2088, found 271.2090.

**4.1.9. Ethyl 3-[*cis*-1,2-diethyl-2-(*tert*-butyldimethylsiloxymethyl)cyclopropyl]acrylate (*cis*-11).** To a 0 °C suspension of NaH (0.45 g, 11.4 mmol) in THF (20 mL) was added a solution of ethyl diethylphosphonoacetate (2.55 g, 11.4 mmol) in THF (10 mL). After stirring for 0.5 h, *cis*-**10** (2.18 g, 8 mmol) in THF (20 mL) was added slowly. The reaction mixture was warmed to room temperature, stirred overnight, and quenched by slow addition of saturated $NH_4Cl$ (40 mL). The mixture was extracted with

EtOAc (50 mL×2). The combined extracts were washed with water (50 mL) and brine (50 mL), dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 40/1) to furnish *cis*-**11** as a colorless oil (1.96 g, 72% yield); $^1$H NMR: $\delta$ 6.98 (d, 1H, $J$=16 Hz), 5.76 (d, 1H, $J$=16 Hz), 4.15–4.22 (q, 2H, $J$=7.5 Hz), 3.67 (d, 1H, $J$=10.5 Hz), 3.27 (d, 1H, $J$=10.5 Hz), 1.41–1.79 (m, 4H), 1.29 (t, 3H, $J$=7.5 Hz), 0.97 (t, 3H, $J$=7.5 Hz), 0.94 (t, 3H, $J$=7.5 Hz), 0.85 (s, 9H), 0.84 (d, 1H, $J$=4.8 Hz), 0.47 (d, 1H, $J$=4.8 Hz), 0.00 (s, 3H), 0.00 (s, 3H); IR (film, cm$^{-1}$): 1720, 1259. Anal. Calcd for $C_{19}H_{36}O_3Si$: C 67.01, H 10.65. Found: C 66.83, H 10.70.

**4.1.10. Ethyl 3-[*trans*-1,2-diethyl-2-(*tert*-butyldimethylsiloxymethyl)cyclopropyl]acrylate (*trans*-11).** It was prepared in the same manner as *cis*-**11**. The crude product resulting from concentration was used without purification. $^1$H NMR: $\delta$ 6.91 (d, 1H, $J$=16.0 Hz), 5.74 (d, 1H, $J$=16.0 Hz), 4.12–4.17 (q, 2H, $J$=7.5 Hz), 3.70 (d, 1H, $J$=10.5 Hz), 3.53 (d, 1H, $J$=10.5 Hz), 1.41–1.73 (m, 4H), 1.26 (t, 3H, $J$=7.5 Hz), 0.91 (t, 3H, $J$=7.5 Hz), 0.86 (s, 9H), 0.85 (t, 3H, $J$=7.5 Hz), 0.74 (d, 1H, $J$=4.8 Hz), 0.61 (d, 1H, $J$=4.8 Hz), 0.01 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR: $\delta$ 166.8, 152.9, 119.7, 63.8, 59.9, 36.2, 33.2, 25.6, 24.2, 24.1, 23.7, 18.0, 14.1, 11.4, 10.9, −5.7, −5.7; IR (film, cm$^{-1}$): 1720 (C═O), 1637, 1258, 1176. Anal. Calcd for $C_{19}H_{36}O_3Si$: C 67.01, H 10.65. Found: C 66.95, H 10.74.

**4.1.11. Diethyl 3-(*cis*-1,2-diethyl-2-hydroxymethylcyclopropyl)acrylate (*cis*-12).** To a solution of *cis*-**11** (68 mg, 0.2 mmol) in THF (2 mL) at 0 °C was added aqueous HCl (3 M, 0.7 mL, 2 mmol). The reaction was warmed to room temperature and stirred until the reactant disappeared (TLC). The reaction mixture was extracted with EtOAc (10 mL×3) and washed with aqueous $NaHCO_3$ (5%, 15 mL) and brine (15 mL). The solution was dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 3/1) to give *cis*-**12** as a colorless oil (43 mg, 95%); $^1$H NMR: $\delta$ 6.98 (d, 1H, $J$=15.6 Hz), 5.82 (d, 1H, $J$=15.6 Hz), 4.15–4.22 (q, 2H, $J$=7.5 Hz), 3.69 (d, 1H, $J$=12.0 Hz), 3.43 (d, 1H, $J$=12.0 Hz), 1.45–1.82 (m, 4H), 1.6–1.8 (1H), 1.29 (t, 3H, $J$=7.5 Hz), 1.00 (t, 3H, $J$=7.5 Hz), 0.94 (t, 3H, $J$=7.5 Hz), 0.88 (d, 1H, $J$=4.8 Hz), 0.56 (d, 1H, $J$=4.8 Hz); IR (film, cm$^{-1}$): 3443 (br s, OH), 1717, 1634, 1179. Anal. Calcd for $C_{13}H_{22}O_3$: C 68.99, H 9.80. Found: C 68.81, H 10.03.

**4.1.12. Diethyl 3-(*trans*-1,2-diethyl-2-hydroxymethylcyclopropyl)acrylate (*trans*-12).** It was prepared in the same manner as *cis*-**12** in 91% yield (two steps); $^1$H NMR: $\delta$ 6.93 (d, 1H, $J$=15.3 Hz), 5.80 (d, 1H, $J$=15.3 Hz), 4.15–4.22 (q, 2H, $J$=7.5 Hz), 3.75 (d, 1H, $J$=12.0 Hz), 3.69 (d, 1H, $J$=12.0 Hz), 2.05 (s, 1H), 1.41–1.80 (m, 4H), 1.30 (t, 3H, $J$=7.5 Hz), 0.94 (t, 3H, $J$=7.5 Hz), 0.93 (t, 3H, $J$=7.5 Hz), 0.84 (d, 1H, $J$=4.8 Hz), 0.69 (d, 1H, $J$=4.8 Hz); $^{13}$C NMR: $\delta$ 166.8, 152.3, 119.9, 63.5, 60.0, 39.5, 33.4, 24.3, 24.0, 23.6, 14.0, 11.5, 10.9; IR (film, cm$^{-1}$): 3449 (br s, OH), 1717, 1635, 1180. Anal. Calcd for $C_{13}H_{22}O_3$: C 68.99, H 9.80. Found: C 68.87, H 9.94; *m*/*z* 227 (M$^+$); HRMS $C_{13}H_{22}O_3Na$ (M$^+$+Na) required 249.1461, found 249.1473.

**4.1.13. Ethyl 3-(*cis*-1,2-diethyl-2-formylcyclopropyl)acrylate (*cis*-13).** It was prepared in a similar manner as *cis*-**10**. Swern oxidation of *cis*-**12** (0.55 g, 2.4 mmol) furnished, after flash chromatography (hexane/EtOAc, 20/1), *cis*-**13** (0.44 g, 82%); $^1$H NMR: $\delta$ 9.06 (s, 1H), 6.93 (d, 1H, $J$=15.6 Hz), 6.91 (d, 1H, $J$=15.6 Hz), 4.16–4.23 (q, 2H, $J$=7.2 Hz), 1.5–2.0 (m, 4H), 1.79 (d, 1H, $J$=5.7 Hz), 1.30 (t, 3H, $J$=7.2 Hz), 1.07 (d, 1H, $J$=5.7 Hz), 0.99 (t, 6H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 201.4, 166.2, 147.8, 123.0, 60.6, 45.4, 38.6, 25.8, 24.5, 20.6, 14.4, 12.1, 11.4; IR (film, cm$^{-1}$): 3454, 1739. Anal. Calcd for $C_{13}H_{20}O_3$: C 69.61, H 8.99. Found: C 69.41, H 9.13; *m*/*z* 224 (M$^+$); HRMS $C_{13}H_{20}O_3$ (M$^+$) required 224.1412, found 224.1375.

**4.1.14. Ethyl 3-(*trans*-1,2-diethyl-2-formylcyclopropyl)acrylate (*trans*-13).** It was prepared in the same manner as *cis*-**13** in 86% yield; $^1$H NMR: $\delta$ 9.46 (s, 1H), 6.99 (d, 1H, $J$=15.9 Hz), 5.99 (d, 1H, $J$=15.9 Hz), 4.21 (q, 2H, $J$=7.2 Hz), 1.58–1.91 (m, 4H), 1.65 (d, 1H, $J$=5.1 Hz), 1.31 (t, 3H, $J$=7.2 Hz), 1.26 (d, 1H, $J$=5.1 Hz), 0.95 (t, 3H, $J$=7.2 Hz), 0.92 (t, 3H, $J$=7.2 Hz); $^{13}$C NMR: $\delta$ 201.3, 166.1, 148.3, 121.9, 60.3, 43.8, 39.3, 25.7, 23.7, 21.6, 14.1, 11.9, 11.7; IR (film, cm$^{-1}$): 1719, 1641, 1459, 1179; *m*/*z* 224 (M$^+$); HRMS $C_{13}H_{20}O_3$ (M$^+$) required 224.1412, found 224.1374.

**4.1.15. (2*Z*,5*Z*)-Ethyl 3,5-diethylcyclohepta-2,5-dienecarboxylate (14).** To a stirred suspension of methyltriphenylphosphonium bromide (268 mg, 0.75 mmol) in THF (2 mL) at 0 °C was added *n*-BuLi (1.6 M in hexane, 0.38 mL, 0.6 mmol). After 0.5 h, a solution of *cis*-**13** (112 mg, 0.5 mmol) in THF (2 mL) was added in one portion. The reaction mixture was allowed to warm to room temperature, stirred overnight, and poured into saturated aqueous $NH_4Cl$ (5 mL), extracted with $Et_2O$ (10 mL×2), dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 40/1) to give **14** as a colorless oil (16 mg, 14% yield); $^1$H NMR: $\delta$ 5.40 (d, 1H, $J$=5.1 Hz), 5.31 (d, 1H, $J$=5.1 Hz), 4.16 (q, 2H, $J$=10.2 Hz), 3.49 (q, 2H, $J$=10.2 Hz), 3.39–3.46 (m, 1H), 2.93 (d, 1H, $J$=17.7 Hz), 2.55 (d, 1H, $J$=17.7 Hz), 2.42 (t, 3H, $J$=6.9 Hz), 1.94–2.09 (m, 4H), 1.01 (t, 3H, $J$=7.2 Hz), 0.99 (t, 3H, $J$=7.5 Hz); IR (film, cm$^{-1}$): 1737, 1462, 1264; *m*/*z* 222 (M$^+$); HRMS $C_{14}H_{22}O_2$ (M$^+$) required 222.1620, found: 222.1621.

**4.1.16. Ethyl 3-(*trans*-1,2-diethyl-2-vinylcyclopropyl)acrylate (*trans*-4).** It was prepared in 76% yield in the same manner as **14** except that the initial temperature was −78 °C; $^1$H NMR: $\delta$ 6.98 (d, 1H, $J$=15.9 Hz), 5.80 (d, 1H, $J$=15.9 Hz), 5.89 (dd, 1H, $J$=15.9, 10.8 Hz), 5.17 (dd, 1H, $J$=10.5, 1.8 Hz), 5.03 (dd, 1H, $J$=10.5, 1.8 Hz), 4.20 (q, 2H, $J$=7.2 Hz), 1.40–1.60 (m, 4H), 1.30 (t, 3H, $J$=7.5 Hz), 0.96 (d, 1H, $J$=4.8 Hz), 0.90 (d, 1H, $J$=4.8 Hz), 0.88 (t, 3H, $J$=7.5 Hz), 0.87 (t, 3H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 166.9, 152.1, 138.7, 120.4, 116.2, 60.1, 38.8, 34.7, 29.7, 26.7, 25.0, 23.7, 14.3, 11.5; IR (film, cm$^{-1}$): 1720, 1636, 1262; *m*/*z* 222 (M$^+$); HRMS $C_{14}H_{22}O_2$ (M$^+$) required 222.1620, found: 222.1616.

**4.1.17. Ethyl 3-(3,5-diethyl-5-vinyl-1,2-dioxolan-3-yl)acrylate (15).** To a stirring solution of the vinylcyclopropane *trans*-**4** (222 mg, 1 mmol) in $CH_3CN$ (10 mL) at 0 °C was

added diphenyl diselenide (32 mg, 0.1 mmol) and AIBN (13 mg, 0.08 mmol). The reaction was placed under a balloon of oxygen and irradiated with a 300 W sunlamp. When starting material was consumed as shown by TLC, the reaction mixture was concentrated in vacuo, and the residue was purified by flash chromatography (hexane/EtOAc, 10/1) to afford **15** as a colorless oil (224 mg, 88%). The cis/trans ratio was shown to be 1/7 by HPLC (Chiralcel AD-H column, 210 nm, hexane/2-propanol, 99/1, flow rate, 0.7 mL/min) $t_R$=9.28, 10.02, 11.13, 12.19 min; *trans*-**15**: $^1$H NMR: $\delta$ 6.86 (d, 1H, $J$=15.9 Hz), 6.05 (d, 1H, $J$=15.9 Hz), 5.79 (dd, 1H, $J$=15.9, 10.8 Hz), 5.26 (dd, 1H, $J$=10.5, 1.8 Hz), 5.17 (dd, 1H, $J$=10.5, 0.9 Hz), 4.20 (q, 2H, $J$=7.2 Hz), 2.59 (d, 1H, $J$=12.3 Hz), 2.37 (d, 1H, $J$=12.3 Hz), 1.56–1.90 (m, 4H), 1.30 (t, 3H, $J$=7.5 Hz), 0.92 (t, 3H, $J$=7.5 Hz), 0.89 (t, 3H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 166.3, 148.4, 138.5, 120.6, 115.2, 88.6, 60.4, 53.4, 30.9, 30.8, 14.1, 8.7, 8.6; *cis*-**15**: $^1$H NMR: $\delta$ 6.98 (d, 1H, $J$=15.9 Hz), 6.11 (d, 1H, $J$=15.9 Hz), 5.87 (dd, 1H, $J$=17.1, 10.8 Hz), 5.29 (dd, 1H, $J$=10.5, 0.9 Hz), 5.21 (dd, 1H, $J$=10.5, 0.9 Hz), 4.21 (q, 2H, $J$=7.5 Hz), 2.53 (d, 1H, $J$=12.3 Hz), 2.43 (d, 1H, $J$=12.3 Hz), 1.56–1.90 (m, 4H), 1.31 (t, 3H, $J$=7.5 Hz), 0.88 (t, 3H, $J$=7.5 Hz), 0.86 (t, 3H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 166.5, 149.3, 140.1, 120.0, 114.3, 87.6, 60.4, 52.6, 30.2, 30.2, 14.1, 8.6, 8.5; IR (film, cm$^{-1}$): 1720, 1657, 1463, 1305; *m/z* 254 ($M^+$); HRMS $C_{14}H_{22}O_4$ ($M^+$) required 254.1518, found: 254.1545.

**4.1.18. *trans*-1,2-Diethyl-1-(*tert*-butyldimethylsiloxymethyl)-2-vinylcyclopropane (*trans*-16).** It was prepared by a similar procedure as employed for **14**, Wittig reaction of *trans*-**10** (4.7 g, 17.4 mmol) furnished, after flash chromatography (hexane), *trans*-**16** (4.44 g, 95%); $^1$H NMR: $\delta$ 5.86 (dd, 1H, $J$=10.5, 17.1 Hz), 5.07 (d, 1H, $J$=1.8, 10.5 Hz), 4.94 (dd, 1H, $J$=1.8, 17.1 Hz), 3.70 (d, 1H, $J$=10.2 Hz), 3.55 (d, 1H, $J$=10.2 Hz), 1.36–1.64 (m, 4H), 0.91 (t, 3H, $J$=7.5 Hz), 0.89 (s, 9H), 0.86 (t, 3H, $J$=7.5 Hz), 0.57 (d, 1H, $J$=4.8 Hz), 0.34 (d, 1H, $J$=4.8 Hz), 0.04 (s, 6H); IR (film, cm$^{-1}$): 1472, 1255, 1083; *m/z* 268 ($M^+$). Anal. Calcd for $C_{16}H_{32}OSi$: C 71.57, H 12.01. Found: C 71.74, H 11.82.

**4.1.19. (*trans*-1,2-Diethyl-2-vinylcyclopropyl)methanol (*trans*-17).** To a solution of *trans*-**16** (3.75 g, 13.7 mmol) in $CH_2Cl_2$/MeOH (15/30 mL) was added *p*-TsOH (0.25 g, 1.4 mmol). The reaction was stirred at room temperature until no starting material remained (TLC). After removal of the solvents, the crude product was purified by column chromatography (hexane/EtOAc, 5/1) to give *trans*-**17** as a colorless oil (1.99 g, 94%); $^1$H NMR: $\delta$ 5.86 (dd, 1H, $J$=10.5, 17.1 Hz), 5.11 (d, 1H, $J$=1.8, 10.5 Hz), 4.97 (dd, 1H, $J$=1.8, 17.1 Hz), 3.68 (q, 2H, $J$=10.2 Hz), 2.09 (s, 1H), 1.57–1.92 (m, 1H), 1.32–1.57 (m, 3H), 0.93 (t, 3H, $J$=7.5 Hz), 0.92 (t, 3H, $J$=7.5 Hz), 0.65 (d, 1H, $J$=4.8 Hz), 0.42 (d, 1H, $J$=4.8 Hz); $^{13}$C NMR: $\delta$ 139.8, 115.1, 64.2, 34.6, 33.6, 25.7, 23.3, 20.7, 11.6, 11.1; IR (film, cm$^{-1}$): 3337; *m/z* 155 ($M^+$+H); HRMS $C_{10}H_{16}$ ($M^+-H_2O$) required 136.1252, found: 136.1244.

**4.1.20. *trans*-1,2-Diethyl-2-vinylcyclopropanecarboxylic acid (*trans*-18).** By a similar procedure as employed for *cis*-**10**, Swern oxidation of *trans*-**17** (2.48 g, 16.1 mmol) furnished a crude aldehyde (2.54 g) that was used without purification in the next step. To a solution of the crude aldehyde (2.54 g, 16 mmol) in *t*-BuOH/$H_2O$ (215/80 mL) was added $KH_2PO_4$ (8 g), resorcinol (2.64 g, 24 mmol), and $NaClO_2$ (2.16 g, 24 mmol). The mixture was stirred at room temperature until all aldehyde was consumed. The aqueous layer was saturated with $NH_4Cl$ and extracted with EtOAc (50 mL×2). The aqueous layer was adjusted to pH 4–5 with 10% HCl, and again extracted with EtOAc (50 mL×2). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 5/1) to give *trans*-**18** as a colorless oil (1.89 g, 70%); $^1$H NMR: $\delta$ 12.03 (br s, 1H), 5.87 (dd, 1H, $J$=10.5, 17.4 Hz), 5.21 (dd, 1H, $J$=1.85, 10.5 Hz), 5.05 (dd, 1H, $J$=1.5, 17.4 Hz), 1.99–2.96 (m, 1H), 1.60–1.76 (m, 1H), 1.42–1.56 (m, 1H), 1.11–1.29 (m, 1H), 1.34 (d, 1H, $J$=4.8 Hz), 0.97 (t, 3H, $J$=7.5 Hz), 0.90 (t, 3H, $J$=7.5 Hz), 0.88 (d, 1H, $J$=4.8 Hz); $^{13}$C NMR: $\delta$ 180.4, 137.7, 117.1, 38.6, 36.6, 25.0, 23.9, 20.9, 11.8, 11.0; IR (film, cm$^{-1}$): 3337, 1689; *m/z* 168 ($M^+$); HRMS $C_{10}H_{16}O_2$ ($M^+$) required 168.1150, found: 168.1131.

**4.1.21. *trans*-1,2-Diethyl-*N*-((*R*)-1-phenylethyl)-2-vinylcyclopropanecarboxamide (*trans*-19).** Oxalyl chloride (0.11 mL, 1.3 mmol, 1.5 equiv) was added dropwise to a solution of *trans*-**18** (0.15 g, 0.89 mmol) in dry $CH_2Cl_2$ (15 mL). The resulting mixture was heated at reflux for 2 h, cooled, and evaporated in vacuo to afford an acid chloride, which was redissolved in dry $CH_2Cl_2$ (10 mL). To the solution was added $Et_3N$ (0.17 mL, 1.2 mmol) and (*R*)-1-methylbenzylamine (0.13 mL, 0.12 g, 1 mmol) under argon at ambient temperature. After stirring for 20 h, the reaction mixture was quenched with water (10 mL), and extracted with $CH_2Cl_2$ (20 mL×3). The combined extracts were washed with 10% $NaHCO_3$ (50 mL) and brine (100 mL). The extracts were dried over $Na_2SO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 5/1) to afford *trans*-**19** as a white powder (0.158 g, 65%); $^1$H NMR: $\delta$ 7.21–7.44 (m, 5H), 5.88 (d, 1H, $J$=7.8 Hz), 5.82 (dd, 0.5H, $J$=10.5, 17.1 Hz), 5.77 (dd, 0.5H, $J$=10.5, 17.1 Hz), 5.13–5.26 (m, 2H), 5.00 (dd, 0.5H, $J$=1.8, 17.1 Hz), 4.99 (dd, 0.5H, $J$=1.8, 17.1 Hz), 1.72–1.95 (m, 1H), 1.57–1.73 (m, 1H), 1.51 (d, 1.5H, $J$=7.2 Hz), 1.50 (d, 1.5H, $J$=7.2 Hz), 1.10–1.31 (m, 2H), 1.07 (d, 1H, $J$=4.8 Hz), 0.94 (t, 3H, $J$=7.5 Hz), 0.87 (t, 3H, $J$=7.5 Hz), 0.71 (d, 1H, $J$=4.8 Hz); $^{13}$C NMR: $\delta$ 171.4, 143.1, 138.0, 128.5 (128.5), 127.3 (127.2), 126.3 (126.2), 116.8, 48.6 (48.6), 39.2 (39.2), 35.6 (35.4), 26.2, 25.5, 25.3, 24.2, 21.4 (21.3), 18.9, 11.7 (11.2), 11.2 (11.1); IR (film, cm$^{-1}$): 3302, 1635, 1536; *m/z* 271 ($M^+$); HRMS $C_{18}H_{25}NO$ ($M^+$) required 271.1936, found: 271.1944.

**4.1.22. *trans*-Methyl 1,2-diethyl-2-vinylcyclopropanecarboxylate (*trans*-20).** An ethereal solution of diazomethane was prepared by stirring a solution of *N*-methylnitrosourea (0.62 g, 6 mmol, 2.0 equiv) in $Et_2O$ (10 mL) with 50% KOH (10 mL) at 0 °C for 30 min. The ethereal layer was separated, dried over solid KOH, and was added dropwise to a stirred solution of *trans*-**18** (0.5 g, 3 mmol) in $Et_2O$ (10 mL) at 0 °C. The reaction mixture was stirred at this temperature under nitrogen for 30 min before the excess of diazomethane was decomposed by the dropwise addition of HOAc. The reaction was then poured into water (20 mL) and the mixture extracted with $Et_2O$ (30 mL×2). The combined ethereal extracts were washed with water (30 mL), 5% $NaHCO_3$ (30 mL), brine (30 mL), dried over

$Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 20/1) to yield *trans*-**20** as a colorless oil (520 mg, 96%); $^1$H NMR: $\delta$ 5.83 (dd, 1H, $J$=10.5, 17.1 Hz), 5.18 (dd, 1H, $J$=1.5, 10.5 Hz), 5.02 (dd, 1H, $J$=1.5, 17.1 Hz), 3.68 (s, 3H), 1.89–2.06 (m, 1H), 1.49–1.64 (m, 1H), 1.22–1.36 (m, 1H), 1.28 (d, 1H, $J$=5.1 Hz), 1.04–1.18 (m, 1H), 0.84 (t, 3H, $J$=7.5 Hz), 0.89 (t, 3H, $J$=7.5 Hz), 0.78 (d, 1H, $J$=5.1 Hz); $^{13}$C NMR: $\delta$ 174.0, 137.9, 116.9, 51.6, 37.2, 25.6, 24.3, 20.4, 12.0, 11.0, 0.9; IR (film, cm$^{-1}$): 1725, 1459, 1261; *m*/*z* 182 ($M^+$); HRMS $C_{11}H_{18}O_2$ ($M^+$) required 182.1307, found: 182.1314.

**4.1.23. *trans*-3-(1,2-Diethyl-2-vinylcyclopropanecarbonyl)oxazolidin-2-one (*trans*-21).** Oxalyl chloride (0.13 mL, 1.5 mmol) was added dropwise to a solution of **18** (0.17 g, 1 mmol) in dry $CH_2Cl_2$ (15 mL). The mixture was heated at reflux for 2 h, cooled, and evaporated in vacuo. Repeated re-evaporation from dry THF afforded the crude acid chloride as a gum. A solution of *n*-BuLi (1.6 M in hexane, 1.3 mL, 2 mmol) was added dropwise over 10 min under argon to a −70 °C solution of oxazolidin-2-one (90 mg, 1 mmol) in dry THF (2 mL). The mixture was stirred at −70 °C for an additional 30 min prior to its addition over 10 min to a solution of the acid chloride obtained above in dry THF (2 mL). Stirring was continued at −70 °C for 1 h. The mixture was then allowed to warm to room temperature overnight (20 h) and concentrated. The residue was diluted with water (10 mL), extracted with EtOAc (15 mL×2) and the combined extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 5/1) to afford *trans*-**21** (176 mg, 75%); $^1$H NMR: $\delta$ 5.98 (dd, 1H, $J$=10.5, 17.1 Hz), 5.22 (dd, 1H, $J$=1.2, 10.5 Hz), 4.98 (dd, 1H, $J$=1.5, 17.1 Hz), 4.37–4.45 (m, 2H), 3.95–4.10 (m, 2H), 2.00–2.17 (m, 2H), 1.70–1.85 (m, 2H), 1.11 (d, 1H, $J$=5.7 Hz), 0.87 (t, 3H, $J$=7.5 Hz), 0.85 (t, 3H, $J$=7.5 Hz), 0.78 (d, 1H, $J$=5.7 Hz); $^{13}$C NMR: $\delta$ 173.3, 152.1, 137.7, 117.1, 61.8, 43.0, 40.0, 37.5, 29.5, 26.7, 23.5, 11.9, 11.0; IR (film, cm$^{-1}$): 1790, 1778, 1682; *m*/*z* 237($M^+$); HRMS $C_{13}H_{19}NO_3Na$ ($M^+$+Na) required 260.1257, found: 260.1257.

**4.1.24. *trans*-(2-(1,2-Diethyl-2-vinylcyclopropyl)vinyl)benzene (*trans*-22).** It was prepared by a similar procedure as employed for *cis*-**10**. Swern oxidation of *trans*-**17** (0.5 g, 3.2 mmol) furnished a crude aldehyde (0.45 g) that was used without purification in the next step. Benzyltriphenylphosphonium bromide (1.73 mg, 4 mmol) was suspended in anhydrous THF (15 mL) under nitrogen. *n*-BuLi (1.6 M in hexane, 2.5 mL, 4 mmol) was added into the reaction flask dropwise at 0 °C. After warming to room temperature, the resulting ylide mixture was allowed to stir for 30 min and then cooled to 0 °C again. A solution of the crude aldehyde (0.45 g, 3 mmol) in THF (10 mL) was added dropwise into the cooled reaction mixture, and was then allowed to warm slowly to room temperature. After 20 h, saturated $NH_4Cl$ (10 mL) was added to the mixture followed by $Et_2O$ (30 mL). The organic layer was separated, and the aqueous layer was extracted with $Et_2O$ (30 mL×2). The combined organic layers were dried over $Na_2SO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (hexane) to afford *trans*-**22** in which the *E*/*Z* ratio is about 3/1 as a colorless oil (0.51 g, 71%); $^1$H NMR: $\delta$ 7.14–7.46 (m, 5H), 6.46 (d, 1H, $J$=12 Hz), 5.90 (dd, 1H, $J$=10.8, 17.1 Hz), 5.78 (d, 1H, $J$=12 Hz), 5.16 (dd, 1H, $J$=1.5, 10.8 Hz), 4.99 (dd, 1H, $J$=1.5, 17.1 Hz), 1.14–1.74 (m, 4H), 1.26 (d, 1H, $J$=4.8 Hz), 0.94 (t, 3H, $J$=7.5 Hz), 0.84 (t, 3H, $J$=7.5 Hz), 0.40 (d, 1H, $J$=4.8 Hz); $^{13}$C NMR: $\delta$ 139.4 (139.7), 137.0 (137.8), 133.3 (132.3), 131.6 (130.6), 129.0 (128.5), 127.8 (126.8), 126.6 (125.9), 115.4 (115.3), 36.6 (35.5), 32.8 (29.7), 27.2 (26.6), 26.5 (26.4), 24.6 (21.2), 12.2 (11.7), 11.6 (11.6); IR (film, cm$^{-1}$): 1640, 1601, 1495, 1463, 1450. Anal. Calcd for $C_{17}H_{22}$: C 90.20, H 9.80. Found: C 90.51, H 9.60; *m*/*z* 226 ($M^+$); HRMS $C_{17}H_{22}$ ($M^+$) required 226.1722, found: 226.1723.

Compounds **23–26** were prepared by a similar procedure as **15**.

**4.1.25. *trans*-3,5-Diethyl-*N*-((*R*)-1-phenylethyl)-5-vinyl-1,2-dioxolane-3-carboxamide (23).** It was obtained as a white powder (quantitative); $^1$H NMR: $\delta$ 7.20–7.40 (m, 5H), 7.15 (d, 0.5H, $J$=8.1 Hz), 7.10 (d, 0.5H, $J$=8.1 Hz), 5.87 (dd, 0.5H, $J$=10.5, 17.1 Hz), 5.83 (dd, 0.5H, $J$=10.5, 17.1 Hz), 5.30 (dd, 0.5H, $J$=0.9, 17.1 Hz), 5.29 (dd, 0.5H, $J$=0.9, 17.1 Hz), 5.20 (dd, 0.5H, $J$=0.9, 10.5 Hz), 5.19 (dd, 0.5H, $J$=0.9, 10.5 Hz), 5.08–5.19 (m, 1H), 2.99 (d, 0.5H, $J$=12.9 Hz), 2.90 (d, 0.5H, $J$=12.9 Hz), 2.49 (d, 0.5H, $J$=12.9 Hz), 2.46 (d, 0.5H, $J$=12.9 Hz), 1.93–2.12 (m, 1H), 1.45–1.83 (m, 3H), 1.52 (d, 1.5H, $J$=6.6 Hz), 1.51 (d, 1.5H, $J$=6.9 Hz), 0.91 (t, 1.5H, $J$=7.5 Hz), 0.89 (t, 1.5H, $J$=7.5 Hz), 0.78 (t, 1.5H, $J$=7.5 Hz), 0.75 (t, 1.5H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 172.3 (172.3), 143.2 (143.0), 140.6 (140.4), 128.8 (128.5), 127.2 (127.1), 126.0 (125.8), 114.1 (141.0), 90.4 (90.4), 88.7 (88.6), 51.2 (50.9), 48.3 (48.4), 29.8 (29.7), 28.7 (28.6), 22.3 (21.7), 8.8 (8.7), 8.4 (8.4); IR (film, cm$^{-1}$): 1654, 1527, 1461; *m*/*z* 304 ($M^+$+H); HRMS $C_{18}H_{25}NO_3Na$ ($M^+$+Na) required 326.1727, found: 326.1724.

**4.1.26. Methyl 3,5-diethyl-5-vinyl-1,2-dioxolane-3-carboxylate (24).** It was obtained as a colorless oil (75%); $^1$H NMR: $\delta$ 5.82 (dd, 1H, $J$=10.8, 17.4 Hz), 5.26 (dd, 1H, $J$=1.5, 17.7 Hz), 5.15 (dd, 1H, $J$=1.5, 11.1 Hz), 3.77 (s, 3H), 2.99 (d, 1H, $J$=12.9 Hz), 2.42 (d, 1H, $J$=12.9 Hz), 1.82 (q, 2H, $J$=7.5 Hz), 1.62 (q, 2H, $J$=7.5 Hz), 0.85 (t, 3H, $J$=7.5 Hz), 0.83 (t, 3H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 173.4, 140.2, 114.1, 89.6, 88.4, 52.4, 50.2, 29.6, 28.2, 8.7, 8.4; IR (film, cm$^{-1}$): 1737, 1461; HRMS $C_{11}H_{18}O_4Na$ ($M^+$+Na) required 237.1097, found: 237.1100.

**4.1.27. 3-(3,5-Diethyl-5-vinyl-1,2-dioxolane-3-carbonyl)-oxazolidin-2-one (25).** It was obtained as colorless crystals (quantitative); HPLC (Chiralcel AD-H column, 214 nm, hexane/2-propanol, 95/5, flow rate, 0.7 mL/min) $t_R$=21.87, 22.95, 24.43, 26.07 min; $^1$H NMR: $\delta$ 5.84 (dd, 1H, $J$=10.8, 17.7 Hz), 5.30 (d, 1H, $J$=17.1 Hz), 5.19 (dd, 1H, $J$=10.8 Hz), 4.44 (t, 2H, $J$=7.5 Hz), 4.01–4.22 (m, 2H), 2.95 (d, 1H, $J$=13.5 Hz), 2.72 (d, 1H, $J$=13.5 Hz), 1.98–2.22 (m, 2H), 1.60 (q, 2H, $J$=7.2 Hz), 0.87 (t, 3H, $J$=7.5 Hz), 0.83 (t, 3H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 172.1, 152.2, 140.2, 114.4, 91.5, 88.3, 62.4, 51.1, 44.0, 29.7, 26.3, 8.6, 8.5; IR (film, cm$^{-1}$): 1796, 1778, 1696, 1479, 1294; *m*/*z* 270 ($M^+$+H), 292 ($M^+$+Na); HRMS

$C_{13}H_{19}NO_5Na$ ($M^+$+Na) required 292.1155, found: 292.1153.

**4.1.28. 3,5-Diethyl-3-styryl-5-vinyl-1,2-dioxolane (26).** It was obtained as a colorless oil (82%), HPLC (Chiralcel AD-H column, 230 nm, hexane/2-propanol, 99.5/0.5, flow rate, 0.3 mL/min) $t_R$=16.68, 15.57, 18.81, 20.05 min; *cis*-**27**: $^1$H NMR: $\delta$ 7.18–7.46 (m, 5H), 6.60 (d, 1H, $J$=16.8 Hz), 6.19 (d, 1H, $J$=16.8 Hz), 5.87 (dd, 1H, $J$=10.5, 17.1 Hz), 5.29 (d, 1H, $J$=17.1 Hz), 5.17 (d, 1H, $J$=10.5 Hz), 2.64 (d, 1H, $J$=12 Hz), 2.38 (d, 1H, $J$=12 Hz), 1.58–1.91 (m, 4H), 0.96 (t, 3H, $J$=7.5 Hz), 0.90 (t, 3H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 142.3, 139.5, 130.9, 129.7, 128.5, 127.6, 126.4, 114.9, 88.6, 88.5, 54.0, 31.6, 31.0, 9.0, 8.8; *trans*-**27**: $^1$H NMR: $\delta$ 7.18–7.46 (m, 5H), 6.64 (d, 1H, $J$=16.8 Hz), 6.22 (d, 1H, $J$=16.8 Hz), 5.89 (dd, 1H, $J$=10.5, 17.1 Hz), 5.31 (d, 1H, $J$=17.1 Hz), 5.19 (d, 1H, $J$=10.5 Hz), 2.52 (s, 2H), 1.58–1.91 (m, 4H), 0.93 (t, 3H, $J$=7.5 Hz), 0.88 (t, 3H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 140.3, 136.8, 131.9, 129.0, 128.6, 127.6, 126.5, 114.2, 88.7, 88.6, 53.4, 31.1, 30.6, 9.0, 8.8; IR (film, cm$^{-1}$): 1732, 1643, 1601, 1495, 1462, 1450; *m/z* 259 ($M^+$+H); HRMS $C_{17}H_{23}O_2$ ($M^+$+H) required 259.1693, found: 259.1705.

**4.1.29. (3,5-Diethyl-1,2-dioxolane-3,5-diyl)dimethanol (27).** To a −78 °C solution of **26** (110 mg, 0.4 mmol) in $CH_2Cl_2$ (4 mL) was bubbled $O_3$. After the mixture turned light blue and TLC analysis displayed little or no starting material, ozonolysis was stopped and the ozone was removed by passage of $O_2$ or $N_2$ through the solution. $NaBH_4$ (15 mg, 0.44 mmol) was added to the reaction mixture at the same temperature and the reaction was slowly (5 h) brought to room temperature. The reaction was diluted with water (2 mL) and the mixture extracted with EtOAc (15 mL×2). The organic extracts were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, 2/1–1/1) to afford firstly *trans*-**27** (45 mg, 59%), followed by *cis*-**27** (16 mg, 21%); *trans*-**27**: $^1$H NMR: $\delta$ 3.72 (d, 2H, $J$=11.7 Hz), 3.42 (d, 2H, $J$=11.7 Hz), 2.22–2.58 (br s, 2H), 2.03 (s, 2H), 1.71–1.88 (m, 2H), 1.46–1.64 (m, 2H), 0.93 (t, 6H, $J$=7.5 Hz); $^{13}$C NMR: $\delta$ 89.4, 64.3, 44.5, 24.9, 9.1; IR (film, cm$^{-1}$): 3372 (br s), 1707, 1463, 1384, 1304; *m/z* 191 ($M^+$+H); HRMS $C_{17}H_{23}O_2$ ($M^+$+Na) required 213.1097, found: 213.1101; *cis*-**27**: $^1$H NMR: $\delta$ 3.74 (d, 2H, $J$=11.7 Hz), 3.46 (d, 2H, $J$=11.7 Hz), 2.6–3.2 (br s, 2H), 2.08 (s, 2H), 1.73–1.88 (m, 2H), 1.50–1.66 (m, 2H), 0.96 (t, 6H, $J$=7.5 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 89.4, 63.8, 44.0, 27.3, 8.6; IR (film, cm$^{-1}$): 3400 (br s), 1450; *m/z* 191 ($M^+$+H); HRMS $C_9H_{18}O_4$ ($M^+$+Na) required 213.1097, found: 213.1097.

## Acknowledgements

The work was supported by the Croucher Foundation (Hong Kong). Q.Z. thanks the Croucher Foundation (Hong Kong) for a Shanghai Studentship. The authors would like to thank Professors Li-Xin Dai, Xue-Long Hou, Xin-Xiang Xu, Tse-Lok Ho, and Dr. Yu-Xue Li for helpful discussion.

## References and notes

1. (a) Patil, A. D.; Freyer, A. J.; Bean, M. F.; Carte, B. K.; Westley, J. W.; Johnson, R. K.; Lahouratate, P. *Tetrahedron* **1996**, *52*, 377; (b) Davidson, B. S. *J. Org. Chem.* **1991**, *56*, 6722; (c) Casteel, D. A. *Nat. Prod. Rep.* **1992**, *9*, 289; (d) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55.
2. (a) Adam, W. *Acc. Chem. Res.* **1979**, *12*, 390; (b) McCullough, K. J. *Contemp. Org. Synth.* **1995**, 225; (c) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601.
3. (a) Bloodworth, A. J.; Courtneidge, J. L. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1807; (b) Bloodworth, A. J.; Chan, K. H.; Cooksey, C. J. *J. Org. Chem.* **1986**, *51*, 2110; (c) Bloodworth, A. J.; Curtis, R. J.; Mistry, N. *J. Chem. Soc., Chem. Commun.* **1989**, 954; (d) Bloodworth, A. J.; Bothwell, B. D.; Collins, A. N.; Maidwell, N. L. *Tetrahedron Lett.* **1996**, *37*, 1885.
4. Ramirez, A.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 4617.
5. (a) Dussault, P. H.; Liu, X.-J. *Org. Lett.* **1999**, *1*, 1391; (b) Dussault, P. H.; Liu, X.-J. *Tetrahedron Lett.* **1999**, *40*, 6553; (c) Dussault, P. H.; Lee, H.-J.; Liu, X.-J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3006; (d) Dussault, P. H.; Trullinger, T. K.; Cho-Shultz, S. *Tetrahedron* **2000**, *56*, 9213; (e) Dussault, P. H.; Lee, I. Q.; Lee, H.-J.; Lee, R. J.; Niu, Q. J.; Schultz, J. A.; Zope, U. R. *J. Org. Chem.* **2000**, *65*, 8408; (f) Dussault, P. H.; Xu, C.-P. *Tetrahedron Lett.* **2004**, *45*, 7455; (g) Dai, P.; Dussault, P. H. *Org. Lett.* **2005**, *7*, 4333; (h) Dai, P.; Trullinger, T. K.; Liu, X.-J.; Dussault, P. H. *J. Org. Chem.* **2006**, *71*, 2283.
6. (a) Feldman, K. S.; Simpson, R. E.; Pravez, M. *J. Am. Chem. Soc.* **1986**, *108*, 1328; (b) Feldman, K. S.; Simpson, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 4878; (c) Feldman, K. S.; Kraebel, C. M. *J. Org. Chem.* **1992**, *57*, 4574; (d) Feldman, K. S. *Synlett* **1995**, 217; (e) Weinreb, C. K.; Hartsough, D.; Feldman, K. S. *Tetrahedron Lett.* **1995**, *36*, 6859.
7. (a) McCoy, L. L. *J. Am. Chem. Soc.* **1958**, *80*, 6568; (b) McCoy, L. L. *J. Org. Chem.* **1960**, *25*, 2078; (c) McCoy, L. L. *J. Am. Chem. Soc.* **1962**, *84*, 2246.
8. Gajewski, J. J.; Hawkins, C. M.; Jimenez, J. L. *J. Org. Chem.* **1990**, *55*, 674.
9. Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669.
10. (a) McDonald, W. S.; Verbicky, C. A.; Zercher, C. *J. Org. Chem.* **1997**, *62*, 1215; (b) Hertweck, C.; Boland, W. *J. Org. Chem.* **2000**, *65*, 2458.
11. Marshall, J. A.; Sedrani, R. *J. Org. Chem.* **1991**, *56*, 5496.
12. Pang, Y. J.; Ritter, H. *Marcromolecules* **2003**, *36*, 7090.
13. Haigh, D.; Birrell, H. C.; Cantello, B. C. C.; Hindley, R. M.; Ramaswamy, A.; Rami, H. K.; Stevens, N. C. *Tetrahedron: Asymmetry* **1999**, *10*, 1335.
14. Hübner, J.; Liebsche, J.; Pätzel, M. *Tetrahedron* **2002**, *58*, 10485.
15. Lin, Y. L.; Turos, E. *J. Org. Chem.* **2001**, *66*, 8751.