Synthetic study toward myrocin analogues. Highly enantio- and diastereo-selective synthesis of a tetracyclic ring system

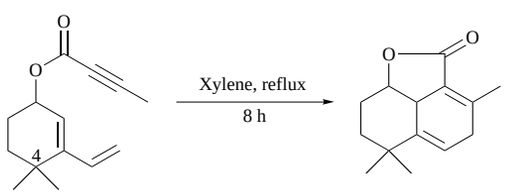
Satoshi Yamada, Shigeru Nagashima, Yumiko Takaoka, Satsuki Torihara, Masakazu Tanaka, Hiroshi Suemune and Mariko Aso *

Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-82, Japan

An intramolecular Diels–Alder reaction for the construction of a lactone ring fused-tricyclic ring system has been developed using propionate as the dienophile. As an application of this reaction, an enantio- and diastereo-selective synthesis of a tetracyclic ring system of a myrocin analogue has been studied.

Diels–Alder reaction to construct a tricyclic system

Intramolecular Diels–Alder reactions using an acetylenic moiety such as a prop-2-ynyl ether or propionate as the dienophile have been considered to be conceptually useful for the construction of ether- or lactone ring-fused tricyclic systems, but there are few examples of its practical use.[1] For example, treatment of compound **1** under thermal conditions afforded the desired product **2** in only 10% yield (Scheme 1).[1c] We considered that one reason for the low reactivity of this system was that the conformation of the diene moiety as s-*cis* was insufficiently fixed even in the presence of geminal dimethyl substituents at the C4-position.



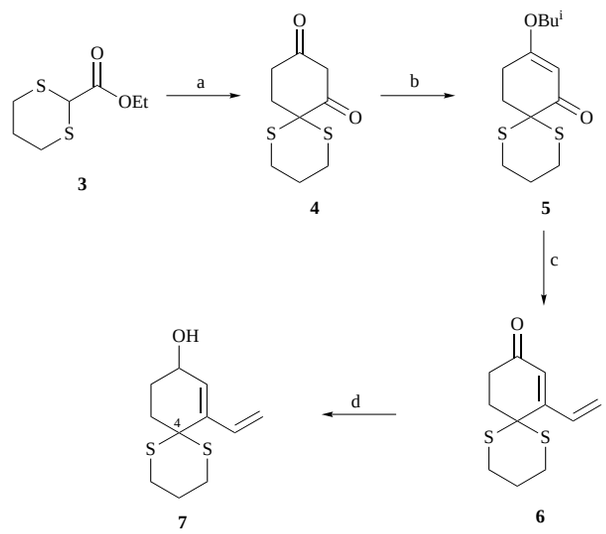
1 **2** (10%)

Scheme 1

Based on this assumption, we designed two types of substrates **8** and **9** (Scheme 3) with a cyclic dithioacetal function at the C4-position, which is a more bulky substituent than those in compound **1**. The synthetic intermediate **7** for the substrates **8** and **9** was prepared starting from ethyl 1,3-dithiane-2-carboxylate **3** by the following sequence of reactions.[2,3] (1) Michael addition of **3** to methyl vinyl ketone (MVK) and subsequent intramolecular cyclization to diketone **4**; (2) regioselective enol ether formation to **5** (63% from **3**); (3) introduction of a vinyl function followed by acid treatment to give **6** (82%); (4) chemoselective reduction of the ketone to give **7** (98%) (Scheme 2).

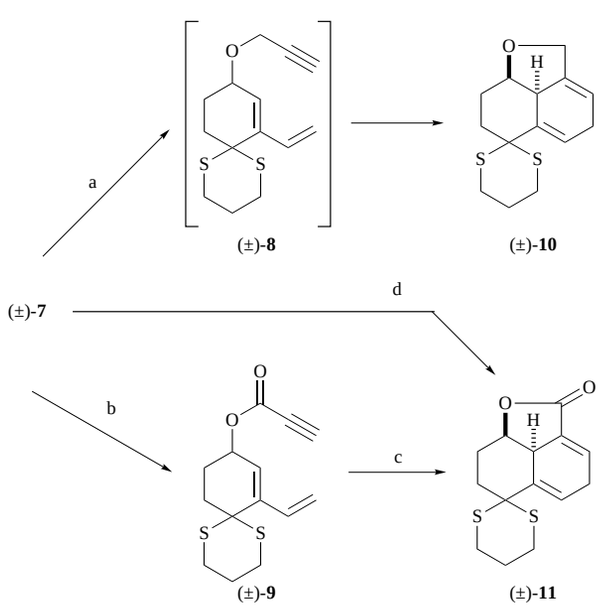
Next, compound **7** was submitted to conditions for ether formation with prop-2-ynyl bromide, however this did not afford the prop-2-ynyl ether **8** but instead gave the cycloaddition product **10** in quantitative yield even at room temperature. The intermediate **8** could not be detected by thin-layer chromatography. On the other hand, acylation of **7** with propiolic acid gave the ester **9** in 80% yield.[4] Diels–Alder reaction of **9** also proceeded smoothly to afford tricyclic lactone **11** in 65% yield. The yield of **11** from **7** was improved to 67% by one-pot conversion without isolation of the intermediate **9** (Scheme 3).

Thus, it was found that, in accord with our expectation, the Diels–Alder reaction of **8** and **9** proceeded smoothly to give the desired **10** and **11**, respectively. The structures of **10** and **11** were determined by spectroscopic analyses. Among those for **11**, a



3 **4** **5** **6** **7**

Scheme 2 *Reagents and conditions*: a, LDA, MVK, THF, −78 °C; b, Bu^{i}OH, *p*-TsOH, benzene, reflux (63% from **3**); c, (i) vinylmagnesium bromide, THF, 0 °C to reflux; (ii) H_2SO_4, 0 °C (82%); d, DIBAL-H, THF, 0 °C (98%)

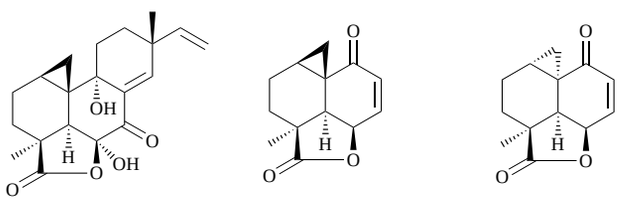


Scheme 3 *Reagents and conditions*: a, prop-2-ynyl bromide, Bu_4NI, aq. NaOH, Et_2O (quant); b, propiolic acid, DCC, DMAP, CH_2Cl_2, 0 °C (80%); c, THF, reflux (65%); d, propiolic acid, DCC, DMAP, toluene, 0 °C to reflux (67%)

signal at 1750 cm^{-1} (γ-lactone carbonyl function) in the IR spectrum and signals of two olefinic protons at δ_H 7.02 (C3-H) and 6.23 (C5-H) in the ^1H NMR spectrum strongly supported the above structure.

These successful results prompted us to undertake a synthetic study of myrocin C related compounds in optically active form. Myrocin C was isolated in 1989 from the culture filtrate of a soil fungus, *Myrothecium verrucaria* strain no. 55.[5] It exhibits half the activity of mitomycin C in an *in vivo* tumor screening. A synthetic study of (±)-myrocin C was first reported by Danishefsky's group.[6]

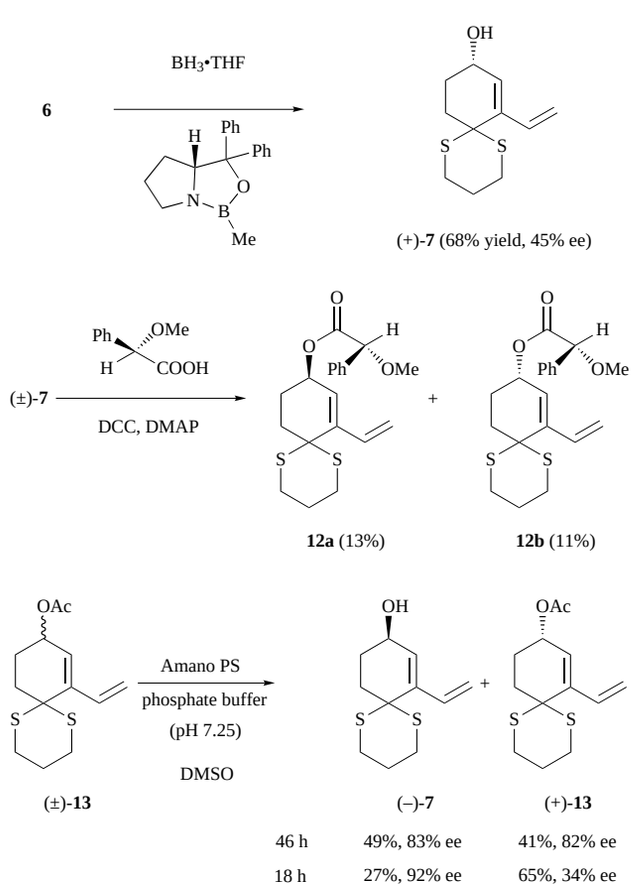
In this work, our attention was focused on the diastereoselective construction of tetracyclic ring systems such as **A** and **B** in an enantiomerically pure form. In particular, we were interested in the stereochemistry of the cyclopropane ring, because this ring system might play an important role in its bioactivity as observed in several other antitumor compounds such as duocarmycin and illudins.[7,8] In addition, compounds of type **A** and **B** might be useful intermediates for the construction of myrocin C related analogues.



myrocin C **A** **B**

Preparation of optically active hydroxydiene 7

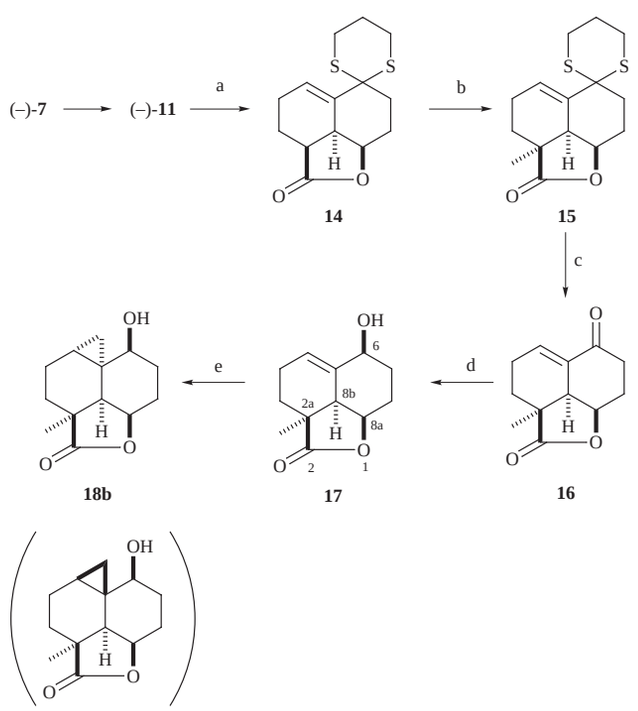
The preparation of optically active hydroxydiene **7** was studied using three methods as shown in Scheme 4. A preliminary study on the enantioselective reduction of the dienone **6** using chiral oxazaborolidine[9] gave (+)-**7** of 45% ee in 68% yield. In the second method, esterification of (±)-**7** using (*R*)-*O*-methylmandelic acid afforded diastereomeric esters **12a**,**b** in poor yields, which were separable by silica-gel column chromatography. The above two methods were not applicable because of their poor efficiency. For the third method, kinetic resolution on enzymatic hydrolysis using Amano PS of (±)-**13** derived from (±)-**7** afforded reasonable results. That is to say, in the case of the reaction for 18 h, (*R*)-(−)-**7** (27% yield, 91% ee) with the desired absolute stereochemistry for further synthetic study was afforded accompanied by (*S*)-acetate (+)-**13** (65% yield, 34% ee). Further prolonging the reaction time to 46 h gave (−)-**7** (49% yield, 83% ee) and (+)-**13** (41% yield, 82% ee). The enantiomeric excess of **7** was determined by high-performance liquid chromatography (HPLC) using a chiral column (Daicel Chiralpac AS) after conversion into the corresponding acetate **13**. Its absolute stereochemistry was determined based on a modified Mosher's method[10] using **12a**,**b**. In the comparison of ^1H NMR spectra of **12a** and **b**, signals of all the olefinic protons in **12b** were observed at higher field than those in **12a**, which shows that **12a** has the *R* configuration and **12b**, the opposite one. The stereogenic correlations for compounds **12**, **7** and **13** were easily clarified by hydrolysis and acetylation.



Scheme 4 Preparation of optically active **7**

Synthetic study of tetracyclic compound B

Starting from (−)-**7** of 92% ee, the synthesis of compounds **A** and **B** was studied (Scheme 5). Compound (−)-**7** was converted into tricyclic (−)-**11** (67%) as shown in Scheme 2. Chemo- and diastereo-selective reduction of the conjugated olefin function in **11** was achieved by treatment with the diimide prepared from 2,4,6-triisopropylbenzenesulfonyl hydrazide (TPSH) and triethylamine[11] to afford **14** in 95% yield. This process was also achieved by reduction with potassium tri-*sec*-butylborohydride (K-Selectride),[12] but the yield of **14** was 62%. Next, quaternary methylation of **14** [lithium diisopropylamide (LDA), MeI] afforded **15** in 84% yield. In the above two-step sequence, no diastereomeric products were detected at all, which might be



Scheme 5 *Reagents and conditions*: a, TPSH, Et_3N, THF–MeOH, rt (95%); b, LDA, THF, MeI, −78 °C to rt (84%); c, $Tl(NO_3)_3 \cdot 3H_2O$, THF–MeOH, rt (52%); d, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, 0 °C (98%); e, Et_2Zn, $ClCH_2I$, CH_2Cl_2, 0 °C to rt (74%)

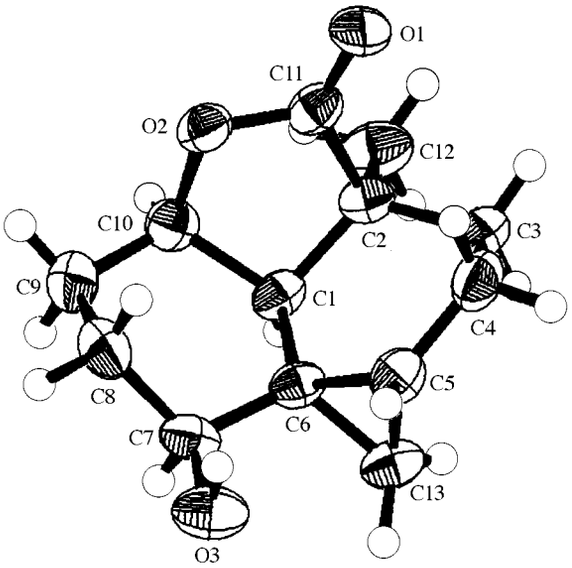
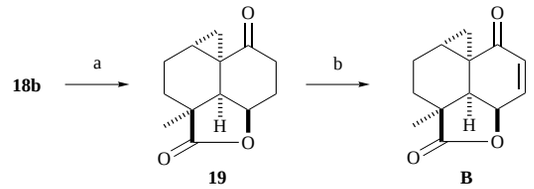


Fig. 1 ORTEP diagram of compound **18b**

due to the high ring strain of diastereomeric *trans*-fused lactone products. The stereochemistry of **14** and **15** was assumed based on a convex approach of the reagent and that of **15** was confirmed after conversion into **17**. Deprotection of the cyclic dithioacetal function in **15** with thallium(III) nitrate[13] gave a conjugate enone **16** in 52% yield. The same reaction with [bis(trifluoroacetoxy)iodo]benzene[14] also gave a similar result, but the reproducibility of this method was poor.

For the diastereoselective construction of the cyclopropane ring, we designed a hydroxy group-directed cyclopropanation. That is to say, 1,2-reduction of **16** with $NaBH_4$ in the presence of $CeCl_3$ gave (6*S*)-hydroxy compound **17** (98%) as the sole product,[15] which was rationalized by the attack of the reagent at the ketone function from the convex face. The stereochemistry of **17** was confirmed by observation of an NOE correlation between C2a-Me and C8a-H, C2a-Me and C8b-H, C8b-H and C6-H. In the next cyclopropanation, we expected that the 6*S*-hydroxy group might direct the diastereoselectivity to the β-cyclopropane derivative **18a**. But, contrary to our expectation, Simmons–Smith reaction[16] of **17** gave the α-cyclopropane derivative **18b** in 74% yield, and formation of the diastereomeric **18a** was not detected at all. The stereochemical structure of **18b** was determined by X-ray analysis, and its ORTEP-diagram is shown in Fig. 1. This result suggested that the contribution of the 6*S*-hydroxy group to the β-diastereoselectivity was less than we had expected because of its equatorial orientation within the highly fixed conformation of the tricyclic system. The dihedral angle of C5–C6–C7–O3 of **17** was very small (−11.43° based on MM2 calculation). The major reason for this α-diastereoselectivity may be attributed to the L-shape of **17** and the consequent convex face approach of the reagent. Although several further attempts were made to construct the β-cyclopropane derivative (**18a**-type) from **16** and **17**, the results were not successful.

Conversion of **18b** into one of the targets **B** was accomplished by the following two-step sequence. (1) PCC oxidation of **18b** into the ketone **19** (98%),[17] (2) enone formation of **B** (69%) from **19** *via* a silyl enol ether by Saegusa's method (Scheme 6).[18] Thus, diastereoselective construction of tetracyclic **B** has been established. Further synthetic study of myrocin analogues from **B** is in progress.



Scheme 6 *Reagents and conditions*: a, PCC, Celite, CH_2Cl_2, rt (98%); b, (i) LDA, THF, TMSCl, −78 °C to rt; (ii) $Pd(OAc)_2$, MeCN, 40 °C (69%)

Experimental

General

Melting points were measured on a Yanaco micro melting point apparatus without correction. ^{1}H NMR spectra were taken on a JEOL GX-270 (270 MHz), JEOL JMN-GX-500 (500 MHz) or Hitachi R-1500 (60 MHz) spectrometer. *J* Values are given in Hz. ^{13}C NMR were recorded on a JEOL GX-270 (67.8 MHz) spectrometer. In the ^{13}C NMR spectra, s, d, t and q refer to quaternary, tertiary, secondary and primary carbons, respectively. Chemical shifts are reported in δ units (parts per million downfield from tetramethylsilane). IR spectra were measured on a JASCO IR A-100 infrared spectrophotometer. Mass spectra (EI and FAB) were measured on a JEOL JMS-D300 or JEOL JMS-SX102 spectrometer. Specific rotations were measured on JASCO DIP-360 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. The elemental analyses were performed on a Yanaco MT2 CHN recorder. Analytical thin-layer chromatography (TLC) was performed with E. M. Merck precoated TLC plates (Kieselgel 60 F254). Column chromatography was carried out on E. M. Merck Kieselgel 60 (70–230 mesh). Solvents were distilled and dried before use. Reactions were carried out under an argon atmosphere if necessary.

9-Isobutoxy-1,5-dithiaspiro[5.5]undec-8-en-7-one 5

To a cooled (−78 °C) solution of LDA, prepared from diisopropylamine (21 ml, 146 mmol) and butyllithium (1.56 M solution in hexane, 95 ml, 146 mmol) in THF (350 ml), was added dropwise a solution of ethyl 1,3-dithiane-2-carboxylate **3** (23.6 g, 122 mmol) in THF (12 ml), and the whole was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C again, and methyl vinyl ketone (15 ml, 183 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 15 min, and then stirred overnight at room temperature. The resulting mixture was treated with water, and the organic layers were concentrated *in vacuo*. The residue was combined with the aqueous layer followed by diethyl ether washing (×2). The aqueous layer was acidified with 10% aqueous H_2SO_4 (pH 1), then extracted with AcOEt (×3). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo* to give the crude diketone **4**. To a suspension of crude **4** in benzene (400 ml) and Bu^iOH (23 ml, 244 mmol) was added *p*-TsOH·H_2O (232 mg, 1.22 mmol), and the whole was refluxed for 2 h using a Dean–Stark apparatus. The reaction mixture was washed with saturated aqueous $NaHCO_3$, and the aqueous layer was re-extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography (hexane–AcOEt, 10 : 1) to give the isobutyl enol ether **5** (20.9 g, 63% from **3**) as colorless plates, mp 94–95 °C (diethyl ether); ν_{max}(KBr)/cm^{-1} 2960, 1640, 1610; δ_H(270 MHz, $CDCl_3$) 5.20 (br s, 1H), 3.60 (d, *J* 6.3, 2H), 3.60–3.49 (m, 2H), 2.67–2.58 (m, 2H), 2.57 (t, *J* 6.3, 2H), 2.28 (t, *J* 6.3, 2H), 2.26–2.17 (m, 1H), 2.07–1.86 (m, 2H), 0.97 (d, *J* 6.8, 6H); *m*/*z* (EI) 272 (M^+, 24.2%), 239 (26.0), 183 (33.9), 132 (100) (Calc. for $C_{13}H_{20}O_2S_2$: C, 57.31; H, 7.40. Found: C, 57.30; H, 7.43%).

7-Vinyl-1,5-dithiaspiro[5.5]undec-7-en-9-one 6

To a cooled (0 °C) solution of vinylmagnesium bromide in THF (1.0 M, 59 ml, 59 mmol) was added a solution of **5** (8.03 g, 29.5 mmol) in THF (30 ml), and the whole was refluxed for 1 h. After cooling to room temperature, the mixture was poured into cooled (0 °C) 10% aqueous H_2SO_4. The mixture was stirred for 15 min at 0 °C. The aqueous layer was extracted with Et_2O (×2), and the combined organic layers were washed with satur-

ated aqueous $NaHCO_3$ and then brine. After removal of the solvent, the residue was purified by column chromatography (hexane–AcOEt, 4:1) to give the dienone **6** (5.47 g, 82%) as a colorless solid, mp 99–100 °C (hexane); ν_{max}(KBr)/cm^{-1} 2970, 1660; δ_H(270 MHz, $CDCl_3$) 6.90 (dd, *J* 17.2, 10.9, 1H), 6.21 (br s, 1H), 5.80 (dd, *J* 17.2, 1.0, 1H), 5.45 (dd, *J* 10.9, 1.0, 1H), 3.16–3.04 (m, 2H), 2.80–2.60 (m, 6H), 2.19–2.09 (m, 1H), 1.98–1.82 (m, 1H); *m*/*z* (EI) 226 (M^+, 34.0%), 200 (80.0), 74 (100) (Calc. for $C_{11}H_{14}OS_2$: C, 58.37; H, 6.23. Found: C, 58.45; H, 6.26%).

7-Vinyl-1,5-dithiaspiro[5.5]undec-7-en-9-ol 7

To a cooled (0 °C) solution of **6** (7.67 g, 33.9 mmol) in THF (100 ml) was added dropwise a solution of diisobutylaluminium hydride (DIBALH) in hexane (0.95 M, 43 ml, 40.7 mmol). The mixture was stirred for 5 min at 0 °C and then sodium fluoride (NaF) (6.83 g, 163 mmol) and water (2.2 ml, 163 mmol) were carefully added. The mixture was vigorously stirred for 30 min at room temperature, filtered through Celite and rinsed with MeOH. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane–AcOEt, 2:1) to afford the alcohol **7** (7.60 g, 98%) as a colorless oil; ν_{max}(neat)/cm^{-1} 3370, 2920; δ_H(270 MHz, $CDCl_3$) 6.70 (ddt, *J* 17.0, 10.7, 0.9, 1H), 6.11 (d, *J* 3.3, 1H), 5.54 (dd, *J* 17.0, 1.6, 1H), 5.13 (dd, *J* 10.7, 1.6, 1H), 4.29 (br t, *J* 7.9, 1H), 3.14–3.02 (m, 2H), 2.72–2.59 (m, 3H), 2.29 (ddd, *J* 14.0, 10.2, 2.8, 1H), 2.16–1.73 (m, 5H); *m*/*z* (EI) 228 (M^+, 33.0%), 135 (100); [HRMS (FAB) Calc. for $C_{11}H_{16}OS_2$: M^+, 228.0643. Found: *M*, 228.0647].

(8a′*RS*,8b′*RS*)-Spiro[1,3-dithiane-2,6′-(4,6,7,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan)] 10

To a solution of **7** (563 mg, 2.47 mmol) in Et_2O (5 ml) was added 50% aqueous NaOH (5 ml), prop-2-ynyl bromide (1.0 ml, 9.88 mmol) and Bu_4NI (274 mg, 0.74 mmol), and the whole was stirred for 10 h. After the mixture was neutralized with 10% aqueous HCl, the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 3:1) to afford the Diels–Alder adduct **10** (657 mg, quant.) as a colorless oil; δ_H(270 MHz, $CDCl_3$) 6.33–6.30 (m, 1H), 5.79–5.76 (m, 1H), 4.46 (ddd, *J* 10.9, 8.6, 4.8, 1H), 4.32–4.31 (dd, *J* 2.6, 1.3, 2H), 3.49–3.26 (m, 1H), 3.09–2.63 (m, 6H), 2.17–1.80 (m, 6H); δ_C(68 MHz, $CDCl_3$) 139.4 (s), 136.8 (s), 126.6 (d), 116.3 (d), 77.0 (d), 69.3 (t), 52.3 (t), 40.8 (d), 36.6 (t), 29.3 (t), 28.4 (t), 27.8 (t), 27.4 (t), 25.0 (t); *m*/*z* (EI) 266 (M^+, 100%).

(*R*)-7-Vinyl-1,5-dithiaspiro[5.5]undec-7-en-9-yl (*R*)-α-methoxyphenylacetate 12a and (*S*)-7-vinyl-1,5-dithiaspiro[5.5]undec-7-en-9-yl (*R*)-α-methoxyphenylacetate 12b

To a solution of **7** (208 mg, 0.91 mmol) and (*R*)-α-methoxyphenylacetic acid (182 mg, 1.09 mmol) in CH_2Cl_2 (10 ml) were successively added *N*,*N*′-dicyclohexylcarbodiimide (DCC) (206 mg, 1.00 mmol) and 4-(dimethylamino)pyridine (DMAP) (11 mg, 0.09 mmol), and the whole was stirred for 20 min at room temperature. The resulting mixture was filtered, and the filtrate was washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 4:1) to give the esters **12a** (41.6 mg, 12%) and **12b** (40.8 mg, 11.7%) each as a colorless oil. **12a**: ν_{max}(neat)/cm^{-1} 2940, 1740; δ_H(500 MHz, $CDCl_3$) 7.46–7.43 (m, 2H), 7.38–7.31 (m, 3H), 6.70 (dd, *J* 17.1, 11.0, 1H), 5.53 (dd, *J* 17.1, 1.2, 1H), 5.37 (br dd, *J* 9.8, 5.5, 1H), 5.15 (dd, *J* 11.0, 1.2, 1H), 4.76 (s, 1H), 3.42 (s, 3H), 3.07–2.98 (m, 2H), 2.65 (ddt, *J* 23.2, 14.6, 3.9, 2H), 2.43 (ddd, *J* 14.0, 9.2, 3.1, 1H), 2.33 (ddd, *J* 14.0, 9.2, 3.1, 1H), 2.11–2.05 (m, 1H), 1.98–1.91 (m, 1H), 1.89–1.79 (m, 1H), 1.72–1.64 (m, 1H); $[a]_D^{25}$ +68.2 (*c* 1.4, $CHCl_3$); **12b**: ν_{max}(neat)/cm^{-1} 2910, 1725; δ_H(500 MHz, $CDCl_3$) 7.46–7.43 (m, 2H), 7.38–7.30 (m, 3H), 6.66 (dd, *J* 17.1, 11.0, 1H), 5.83 (d, *J* 3.7, 1H), 5.39 (dd, *J* 17.1, 1.6, 1H), 5.36 (br dd, *J* 9.8, 5.5, 1H), 5.09 (dd, *J* 11.0, 1.6, 1H), 4.76 (s, 1H), 3.41 (s, 3H), 3.10–3.01 (m, 2H), 2.66 (ddt, *J* 18.9, 14.7, 3.8, 1H), 2.57 (ddd, *J* 14.7, 9.2, 2.8, 1H), 2.38 (ddd, *J* 14.0, 9.2, 2.8, 1H), 2.14–2.05 (m, 2H), 1.93–1.80 (m, 2H); $[a]_D^{25}$ +68.2 (*c* 1.4, $CHCl_3$).

7-Vinyl-1,5-dithiaspiro[5.5]undec-7-en-9-yl acetate 13

The crude alcohol **7** obtained from dienone **6** (1.54 g, 6.81 mmol) was used for the preparation of acetate **13**. To a solution of crude **7** in THF (35 ml) was added acetic anhydride (0.95 ml, 10.2 mmol) and 4-(dimethylamino)pyridine (DMAP) (250 mg, 2.04 mmol) and the mixture stirred for 20 min at room temperature. The resulting mixture was washed with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 5:1) to give acetate **13** (1.74 g, 95% from **7**) as a colorless oil, ν_{max}(neat)/cm^{-1} 2930, 1720; δ_H(270 MHz, $CDCl_3$) 6.71 (ddt, *J* 17.2, 1.9, 0.9, 1H), 6.05 (br d, *J* 3.6, 1H), 5.55 (dd, *J* 17.2, 1.6, 1H), 5.33 (br dd, *J* 9.6, 5.6, 1H), 5.15 (dd, *J* 10.9, 1.6, 1H), 3.08 (ddq, *J* 14.5, 12.5, 3.0, 2H), 2.74–2.54 (m, 3H), 2.40 (ddd, *J* 14.2, 9.2, 3.0, 1H), 2.16–2.00 (m, 2H), 2.07 (s, 3H), 1.95–1.81 (m, 2H); *m*/*z* (EI) 270 (M^+, 54.3%), 211 (100); [HRMS (FAB) Calc. for $C_{13}H_{18}O_2S_2$: M^+, 270.0749. Found: *M*, 270.0745].

Lipase-catalyzed hydrolysis of (±)-acetate 13

To a solution of (±)-acetate **13** (200 mg) in DMSO (4 ml) was added 0.1 M phosphate buffer (pH 7.25) and Amano Lipase PS (200 mg) and the mixture was incubated at 33 °C. The resulting mixture was passed through Celite followed by Et_2O washing. The aqueous layer was extracted with Et_2O (×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 5:1 to 2:1) to give alcohol **7** and acetate **13**. The enantiomeric excess was determined by HPLC (column: Daicel Chiralpac AS, eluent: hexane–Pr^{i}OH, 99:1; flow rate: 1.0 ml min^{-1}, detection: 254 nm) after conversion into corresponding acetate: alcohol **7** (91% ee); $[a]_D^{26}$ −11.3 (*c* 0.59, $CHCl_3$); acetate **13** (34% ee); $[a]_D^{28}$ −17.6 (*c* 0.55, $CHCl_3$).

(8a′*R*,8b′*S*)-Spiro[1,3-dithiane-2,6′-(4,6,7,8,8a,8b-hexahydro-2*H*-naphtho[1,8-*bc*]furan)]-2′-one 11

To a cooled (−10 °C) solution of alcohol **7** (8.42 g, 36.9 mmol) and propiolic acid (2.3 ml, 36.9 mmol) in toluene (190 ml) was added dropwise a solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (9.15 g, 44.2 mmol) and 4-(dimethylamino)pyridine (DMAP) (450 mg, 3.69 mmol). The mixture was stirred for 30 min at room temperature and then additional propiolic acid (2.3 ml, 36.9 mmol), DCC (4.58 g, 22.1 mmol) and DMAP (450 mg, 3.69 mmol) were successively added. The resulting mixture was stirred for 15 min, and then refluxed for 1 h. After cooling to room temperature, the mixture was passed through a short column on silica gel, which then was eluted with hexane–Et_2O, 1:2. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane–Et_2O, 3:2) to give the Diels–Alder adduct **11** (6.90 g, 67%) as a colorless viscous oil, ν_{max}(neat)/cm^{-1} 1750; δ_H(270 MHz, $CDCl_3$) 7.04–6.99 (m, 1H), 6.26–6.20 (m, 1H), 5.02 (ddd, *J* 12.5, 8.5, 4.0, 1H), 3.73–3.63 (m, 1H), 3.29–2.92 (m, 3H), 2.80–2.61 (m, 3H), 2.12–1.82 (m, 5H), 1.63–1.24 (m, 1H); δ_C(68 MHz, $CDCl_3$) 168.8 (s), 136.4 (s), 134.9 (d), 129.5 (s), 125.4 (d), 76.2 (d), 51.2 (s), 39.9 (d), 36.8 (t), 29.33 (t), 29.28 (t), 27.9 (t), 26.6 (t), 24.4 (t); *m*/*z* (EI) 282 (MH^+, 100%) [HRMS (FAB) Calc. for $C_{14}H_{16}O_2S_2$: M^+, 280.0591. Found: *M*, 280.0586]; $[a]_D^{28}$ −79.7 (*c* 0.54, $CHCl_3$).

(2a′*S*,8a′*R*,8b′*S*)-Spiro[1,3-dithiane-2,6′-(2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan)]-2′-one 14

To a solution of **11** (5.32 g, 19.9 mmol) in THF (70 ml) and MeOH (70 ml) was added 2,4,6-triisopropylbenzenesulfonyl hydrazide (19.8 g, 66.4 mmol) and triethylamine (9.3 ml, 66.4

mmol) at room temperature. The mixture was stirred for 12 h at room temperature and then K_2CO_3 (5.25 g, 38.0 mmol) was added. The whole was concentrated *in vacuo*. The residue was diluted with water and extracted with CH_2Cl_2 (×3). The combined organic layers were washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine. The combined aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 4:1) to give **14** (5.11 g, 95%) as colorless needles, mp 165–166 °C (AcOEt); ν_{max}(KBr)/cm^{-1} 2940, 2900, 1765; δ_H(270 MHz; $CDCl_3$) 6.36 (br s, 1H), 4.59 (m, 1H), 3.44–3.40 (m, 1H), 3.05–2.94 (m, 2H), 2.77–2.57 (m, 3H), 2.40–1.88 (m, 8H), 1.78–1.63 (m, 2H); δ_C(68 MHz, $CDCl_3$) 177.8 (s), 131.7 (s), 129.9 (d), 78.4 (d), 54.3 (s), 41.8 (d), 37.6 (d), 34.5 (t), 27.5 (t), 26.3 (t), 25.7 (t), 23.1 (t), 21.7 (t), 18.4 (t); *m*/*z* (EI) 282 (M^+, 100%) (Calc. for $C_{14}H_{18}O_2S_2$: C, 59.54; H, 6.42. Found: C, 59.45; H, 6.47%); $[\alpha]_D^{26}$ −54.7 (*c* 0.11, $CHCl_3$).

(2a′*S*,8a′*R*,8b′*S*)-2a′-Methylspiro[(2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan)]-2′-one 15

To a cooled (−78 °C) solution of LDA, prepared from diisopropylamine (7.1 ml, 50.2 mmol) and butyllithium (1.56 M solution in hexane, 32 ml, 50.2 mmol) in THF (250 ml) was added dropwise a solution of **14** (4.73 g, 16.8 mmol) in THF (170 ml), and the whole was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C again, iodomethane (6.3 ml, 101 mmol) was added dropwise and then the mixture was allowed to warm to room temperature over 1 h. The reaction was quenched by the addition of water and extracted with CH_2Cl_2 (×2). The combined organic layers were washed with saturated aqueous NH_4Cl and brine. The combined aqueous layers were re-extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 5:1) to afford **15** (4.16 g, 84%) as colorless needles, mp 146–148 °C (diethyl ether); ν_{max}(KBr)/cm^{-1} 2950, 2940, 1775; δ_H(270 MHz, $CDCl_3$) 6.43 (br s, 1H), 2.63 (ddd, *J* 14.7, 9.8, 3.1, 1H), 2.33–2.20 (m, 3H), 2.10–1.93 (m, 6H), 1.53–1.46 (m, 1H), 1.34 (s, 3H); δ_C(68 MHz, $CDCl_3$) 180.2 (s), 130.0 (d), 76.7 (d), 54.6 (s), 44.8 (s), 44.1 (d), 34.8 (t), 28.0 (t), 27.5 (t), 26.4 (t), 25.7 (t), 23.3 (t), 22.4 (t), 22.3 (q); *m*/*z* (EI) 296 (M^+, 100%) (Calc. for $C_{15}H_{20}O_2S_2$: C, 60.78; H, 6.80. Found: C, 60.64; H, 6.86%); $[\alpha]_D^{26}$ −83.7 (*c* 0.11, $CHCl_3$).

(2a*S*,8a*R*,8b*R*)-2a-Methyl-2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-2,6-dione 16

To a solution of **15** (8.54 g, 28.8 mmol) in THF (145 ml) and MeOH (145 ml) was added a solution of thallium(III) nitrate trihydrate (29.4 g, 66.3 mmol) in MeOH (60 ml) at room temperature. After being stirred for 5 min, the reaction mixture was filtered through a Florisil column, which was then eluted with AcOEt. The filtrate was concentrated *in vacuo*. The residue was diluted with water and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 2:1) to give the enone **16** (3.11 g, 52%) as a colorless solid, mp 98–100 °C (diethyl ether); ν_{max}(KBr)/cm^{-1} 2970, 2720, 1765, 1700, 1640; δ_H(270 MHz, $CDCl_3$) 6.93 (br s, 1H), 5.11 (dd, *J* 14.5, 7.9, 1H), 2.87 (dt, *J* 8.9, 3.3, 1H), 2.66–2.35 (m, 3H), 2.30–2.22 (m, 2H), 2.17–2.08 (m, 1H), 1.78–1.43 (m, 2H), 1.41 (s, 3H); δ_C(68 MHz, $CDCl_3$) 199.4 (s), 179.4 (s), 138.7 (d), 132.0 (s), 74.9 (d), 43.2 (d), 42.6 (s), 34.4 (t), 27.7 (t), 24.9 (t), 23.8 (q), 22.2 (t); *m*/*z* (EI) 206 (M^+, 39.5%), 161 (100) (Calc. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.91. Found: C, 69.61; H, 6.94%); $[\alpha]_D^{25}$ −136.8 (*c* 1.14, $CHCl_3$).

(2a*S*,6*S*,8a*R*,8b*R*)-6-Hydroxy-2a-methyl-2a,3,4,6,7,8,8a,8b-octahydro-2*H*-naphtho[1,8-*bc*]furan-2-one 17

To a cooled (0 °C) solution of **16** (121 mg, 0.59 mmol) in EtOH (10 ml) was added cerium(III) chloride heptahydrate (219 mg, 0.59 mmol) and sodium borohydride (22.3 mg, 0.59 mmol) at 0 °C. After being stirred for 30 min at 0 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl and the whole was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt 1:1) to give the allyl alcohol **17** (120 mg, 98%) as colorless needles, mp 114–115 °C (toluene); ν_{max}(KBr)/cm^{-1} 3220, 2910, 1750; δ_H(500 MHz, $CDCl_3$) 6.00 (br s, 1H), 4.75–4.72 (m, 1H), 4.02–3.99 (m, 1H), 2.53 (br s, 1H), 2.28 (ddt, *J* 15.3, 4.3, 2.3, 1H), 2.16–2.03 (m, 3H), 1.97–1.80 (m, 3H), 1.56–1.47 (m, 2H), 1.33 (s, 3H); δ_C(68 MHz, $CDCl_3$) 180.5 (s), 135.2 (s), 120.7 (d), 76.2 (d), 70.8 (d), 46.5 (d), 44.9 (s), 31.6 (t), 28.1 (t), 25.6 (t), 22.2 (q), 21.4 (t); *m*/*z* (EI) 208 (M^+, 2.6%), 190 (17.0), 145 (100) (Calc. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.99; H, 7.78%); $[\alpha]_D^{26}$ −45.5 (*c* 0.92, $CHCl_3$).

(2a*S*,5*R*,5a*R*,6*S*,8a*R*,8b*R*)-6-Hydroxy-2a-methyl-2a,3,4,5,5a,-6,7,8,8a,8b-decahydro-2*H*-cyclopropa[4,4a]naphtho[1,8-*bc*]-furan-2-one 18b

To a cooled (0 °C) solution of **17** (637 mg, 3.06 mmol) in CH_2Cl_2 (40 ml) was added dropwise diethylzinc (1.0 M solution in hexane, 24.5 ml, 24.5 mmol) and chloroiodomethane (1.8 ml, 24.5 mmol) at 0 °C. After being stirred for 36 h at room temperature, the reaction was quenched with water and 10% aqueous HCl and the whole was extracted with $CHCl_3$. The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 2:1) to give **18b** (504 mg, 74%) as colorless plates, mp 132–135 °C (diethyl ether); ν_{max}(KBr)/cm^{-1} 3500, 2950, 2875, 1750; δ_H(270 MHz, $CDCl_3$) 4.62–4.57 (m, 1H), 3.63 (dd, *J* 11.4, 3.2, 1H), 2.41 (d, *J* 5.3, 1H), 2.33 (ddd, *J* 14.9, 5.7, 3.1, 1H), 1.89–1.44 (m, 6H), 1.35–1.23 (m, 3H), 1.21 (s, 3H), 0.69 (dd, *J* 8.9, 4.8, 1H), 0.23 (t, *J* 4.8, 1H); δ_C(68 MHz, $CDCl_3$) 180.9 (s), 78.4 (d), 70.2 (d), 45.7 (d), 45.5 (s), 27.1 (t), 27.1 (t), 26.6 (t), 24.4 (q), 21.3 (s), 19.4 (t), 13.9 (d), 8.8 (t); *m*/*z* (EI) 222 (M^+, 8.9%), 204 (54.8), 118 (100) (Calc. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.04; H, 8.17%); $[\alpha]_D^{22}$ −65.2 (*c* 0.12, $CHCl_3$).

(2a*S*,5*R*,5a*R*,8a*R*,8b*R*)-2a-Methyl-2a,3,4,5,5a,6,7,8,8a,8b-decahydro-2*H*-cyclopropa[4,4a]naphtho[1,8-*bc*]furan-2,6-dione 19

To a solution of **18b** (164 mg, 0.74 mmol) in CH_2Cl_2 (15 ml) was added Celite (1.1 g) and pyridinium chlorochromate (PCC) (320 mg, 1.48 mmol) at room temperature. After being stirred for 2 h at room temperature, the resulting mixture was passed through a Florisil column, which was then eluted with Et_2O. The filtrate was concentrated *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 2:1) to give the ketone **19** (159 mg, 98%) as colorless plates, mp 105–106 °C (diethyl ether); ν_{max}(KBr)/cm^{-1} 2930, 2855, 1760, 1685; δ_H(270 MHz, $CDCl_3$) 4.94–4.89 (m, 1H), 2.65–2.14 (m, 5H), 1.97–1.69 (m, 4H), 1.45–1.32 (m, 2H), 1.28 (s, 3H), 0.65 (dd, *J* 7.3, 4.3, 1H); δ_C(68 MHz, $CDCl_3$) 207.6 (s), 179.9 (s), 74.0 (d), 45.7 (d), 43.3 (s), 33.1 (t), 30.0 (d), 27.5 (s), 26.3 (t), 25.3 (t), 24.4 (q), 19.0 (t), 17.9 (t); *m*/*z* (EI) 220 (M^+, 100%) (Calc. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.70; H, 7.34%); $[\alpha]_D^{25}$ −3.31 (*c* 0.71, $CHCl_3$).

(2a*S*,5*R*,5a*R*,8a*R*,8b*R*)-2a-Methyl-2a,3,4,5,5a,6,8a,8b-octahydro-2*H*-cyclopropa[4,4a]naphtho[1,8-*bc*]furan-2,6-dione B

To a cooled (−78 °C) solution of LDA, prepared from diisopropylamine (70 μl, 0.46 mmol) and butyllithium (1.56 M solution in hexane, 0.3 ml, 0.46 mmol) in THF (1.5 ml), was added dropwise a solution of **19** (33.6 mg, 0.15 mmol) in THF (1.0 ml), and the whole was stirred for 30 min at 0 °C. The mixture was cooled to −78 °C again and then chlorotrimethyl-

silane (80 μl, 0.61 mmol) was added dropwise. After being stirred for 2 h at room temperature, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with Et_2O (×2). The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by short column chromatography (hexane–AcOEt, 5:1) to afford the crude silyl enol ether.

To a hot (40 °C) solution of palladium(II) acetate (37 mg, 163 μmol) in CH_3CN (2.5 ml) was added dropwise a solution of the silyl enol ether in CH_3CN (2.5 ml), and the whole was stirred for 4 h. The reaction mixture was washed with 10% aqueous HCl and extracted with AcOEt (×2). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 2:1) to give the enone **B** (22.8 mg, 69%) as colorless solids, ν_{max}(KBr)/cm^{-1} 2920, 2860, 1760, 1660, 1630; δ_H(270 MHz, $CDCl_3$) 7.00 (dd, *J* 10.2, 5.5, 1H), 6.35 (d, *J* 10.2, 1H), 5.09 (dd, *J* 5.5, 5.1, 1H), 2.86 (d, *J* 6.1, 1H), 1.98 (dt, *J* 14.2, 3.5, 1H), 1.92–1.78 (m, 3H), 1.77–1.65 (m, 1H), 1.45–1.21 (m, 1H), 1.31 (s, 3H), 0.82 (dd, *J* 6.8, 3.8, 1H); δ_C(68 MHz, $CDCl_3$) 195.9 (s), 178.6 (s), 137.6 (d), 133.8 (d), 69.5 (d), 43.3 (s), 43.1 (d), 29.8 (d), 26.5 (t), 26.3 (s), 25.0 (t), 24.7 (q), 19.0 (t); *m*/*z* (EI) 218 (M^+, 100%) (Calc. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.86; H, 6.50%); $[\alpha]_D^{25}$ +43.1 (*c* 0.33, $CHCl_3$).

Crystal structure determination of compound 18b

A colorless needle was mounted on a glass fiber and transferred to the diffractometer.

Crystal data. $C_{13}H_{18}O_3$, $M = 222.28$. Orthorhombic, $a = 10.147(3)$, $b = 15.373(4)$, $c = 7.251(2)$ Å, $V = 1131.1(5)$ Å^3 [from centering angles for 24 reflections ($35 \leqslant 2\theta \leqslant 79°$, $\lambda = 1.541\,84$ Å, $T = 298$ K)], space group $P2_12_12_1$ (No. 19), $Z = 4$, $D_x = 1.300$ g cm^{-3}, colorless needle $0.40 \times 0.10 \times 0.10$ mm, μ(Cu-Kα) = 0.74 mm^{-1}.

Data collection and processing. Rigaku AFC5R four-circle diffractometer with rotating anode X-ray generator, ω–2θ scans with ω scan width $(0.89 + 0.30 \tan \theta)°$, filtered Cu-Kα X-radiation; 1020 reflections measured ($2\theta_{max} = 120°$), giving 733 with $F \geqslant 6\sigma(F)$. No crystal decay was observed. Corrections for absorption (range 0.689–1.00) were applied using DIFABS.[19]

Structure solution and refinement. Automatic direct methods[20] (all non-H atoms). Full-matrix least-squares refinement[21] with all non-H atoms anisotropic; hydrogen atoms were located from a ΔF synthesis and freely refined. The weighting scheme selected gave satisfactory agreement analyses. Final $R_1 = 0.045$, $R_w = 0.057$, GOF = 1.28 for 218 refined parameters. The final ΔF synthesis showed no peaks above 0.16 e Å^{-3}.

Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/191.

References

1 (*a*) T.-T. Lie and T.-L. Wu, *Tetrahedron Lett.*, 1988, **29**, 4039; (*b*) Z.-Y. Liu, X.-R. Zhou and Z.-M. Wu, *J. Chem. Soc.*, *Chem. Commun.*, 1987, 1868; (*c*) R. L. Funk, C. J. Mossman and W. E. Zeller, *Tetrahedron Lett.*, 1984, **25**, 1655.
2 E. L. Eliel and A. A. Hartman, *J. Org. Chem.*, 1972, **37**, 505.
3 (*a*) P. C. B. Page and M. B. van Niel, *J. Chem. Soc.*, *Chem. Commun.*, 1987, 43; (*b*) P. C. B. Page, M. B. van Niel and D. Westwood, *J. Chem. Soc.*, *Perkin Trans. 1*, 1988, 269; (*c*) P. C. B. Page, S. A. Harkin, A. P. Marchington and M. B. van Niel, *Tetrahedron*, 1989, **45**, 3819; (*d*) P. C. B. Page, S. A. Harkin and A. P. Marchington, *Tetrahedron Lett.*, 1989, **30**, 7235; (*e*) P. C. B. Page, A. P. Marchington, L. J. Graham, S. A. Harkin and W. W. Wood, *Tetrahedron*, 1993, **49**, 10 369.
4 L. Balas, B. Jousseaume and B. Langwost, *Tetrahedron Lett.*, 1989, **30**, 4525.
5 M. Nakagawa, Y.-H. Hsu, A. Hirota, S. Shima and M. Nakayama, *J. Antibiot.*, 1989, **42**, 218.
6 (*a*) M. Y. Chu-Moyer and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1992, **114**, 8333; (*b*) M. Y. Chu-Moyer, S. J. Danishefsky and G. K. Shulte, *J. Am. Chem. Soc.*, 1994, **116**, 11 213.
7 D. L. Boger, D. S. Johnson and W. Yun, *J. Am. Chem. Soc.*, 1994, **116**, 1635.
8 T. C. McMorris, M. J. Kelner, W. Wang, L. A. Estes, M. A. Montoya and R. Taetle, *J. Org. Chem.*, 1992, **57**, 6876.
9 E. J. Corey and R. K. Bakshi, *Tetrahedron Lett.*, 1990, **31**, 6275 and the preceding paper.
10 I. Ohtami, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
11 N. J. Cusack, C. B. Reese, A. C. Risius and B. Roozpeikar, *Tetrahedron*, 1976, **32**, 2157.
12 J. M. Fortunato and B. Ganem, *J. Org. Chem.*, 1976, **41**, 2194.
13 E. Fujita, Y. Nagao and K. Kaneko, *Chem. Pharm. Bull.*, 1978, **26**, 3743.
14 G. Stork and K. Zhao, *Tetrahedron Lett.*, 1989, **30**, 287.
15 A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.
16 S. E. Denmark and J. P. Edwards, *J. Org. Chem.*, 1991, **56**, 6974.
17 E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647.
18 Y. Ito, T. Hirano and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011.
19 N. Walker and D. Stuart, *Acta Crystallogr.*, *Sect. A*, 1983, **39**, 158.
20 A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi and G. Polidori, SIR92, *J. Appl. Crystallogr.*, 1994, **27**, 435.
21 Molecular Structure Corporation, 3200 Research Forest Drive, The Woodlands, TX 77381, USA TEXSAN Crystal Structure Analysis Package, 1985 and 1992.

Paper 7/08497H
Received 25*th November* 1997
Accepted 13*th January* 1998