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Double Michael Reaction of Wieland-Miescher Ketone

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Abstract: Enolate of Wieland-Miescher ketone **1** has reacted with methyl acrylate to give methyl (1*S**,2*S**,4*R**,6*S**)-6-methyltricyclo[6.2.2.$0^{1,6}$]-dodecan-7,12-dion-2-carboxylate **5** whose structure has been determined by X-ray crystallography after transformation of **5** into sultamamide **8a**.

Construction of complex molecular architecture by multi-bond formation in one pot operation has been one of current interest in synthetic organic chemistry.[1] Among various possibilities by using cationic, anionic, radical, photochemical, thermal or organometallic reaction *etc.*, successive carbon-carbon bond forming reaction initiated by inter- or intra-molecular Michael reaction has provided a versatile process for making carbocyclic compounds.[2] Especially, annulation by successive Michael-Michael procedure (double Michael reaction) has been useful with wide applicability. In order that Michael reaction proceeds successively, proton transfers between enolate and substrate must be suppressed because Michael reaction is essentially reversible. Reaction in aprotic media at low temperature fulfils such requirement. Since at least one intramolecular Michael reaction is required for annulation, initial Michael donor is desired to be bifunctional having ability as a Michael accepter also. Toward this end, regio- and/or chemoselective generation of enolate is needed on the initial Michael donor.

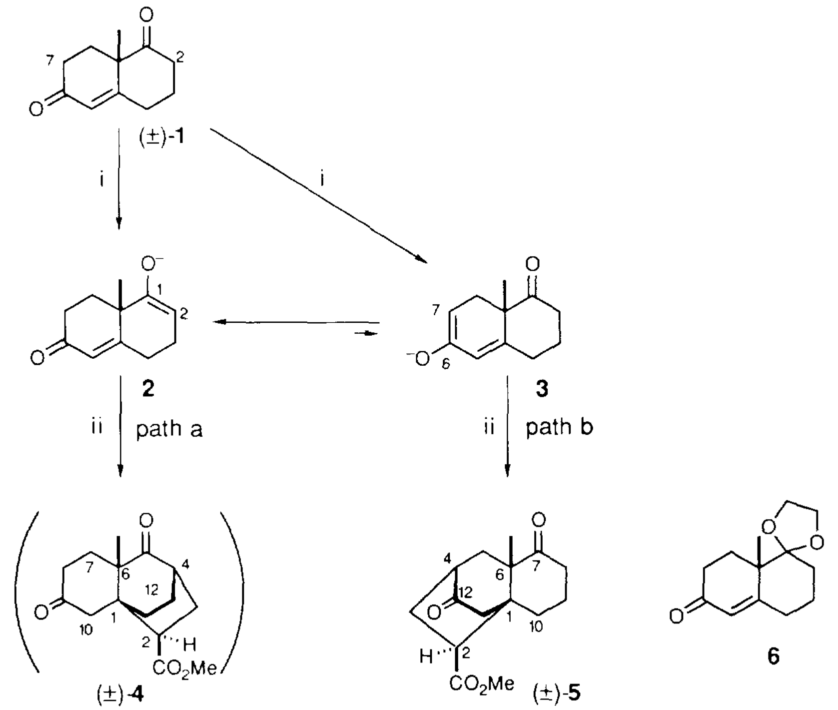
Wieland-Miescher ketone **1** is a good candidate for such purpose due to its bifunctionality for Michael reaction. Some years ago, Grieco *et al.* have reported that by treatment with lithium diisopropylamide (LDA) Wieland-Miescher ketone **1** gave selectively $\Delta^{1,2}$-enolate **2** which reacted with several electrophiles to give *C*- or *O*-alkylated products either in the presence or absence of hexamethylphosphoric triamide (HMPA).[3]

1 **2**

(Ref 3)

We anticipated that the reaction of the $\Delta^{1,2}$-enolate **2** with α,β-unsaturated carbonyl compounds could lead to tricyclic compound **4** after successive two Michael reactions (Scheme 1). Enolate generated by treating Wieland-Miescher ketone (±)-**1** with LDA at 0 °C[4] reacted with methyl acrylate to provide ester (±)-**5** in 28% yield as a sole isolable product. Structure of the product of present reaction could not be determined rigorously, because it was difficult to discriminate the structure of the ester (±)-**5** from another plausible structure of the ester (±)-**4** by spectroscopic means. An attempt to get the ester (±)-**5** by alternative route have failed, in which monoprotected Wieland-Miescher ketone (±)-**6** did not give any annulation product contrary to the successful result of similar system.[5]

Scheme 1

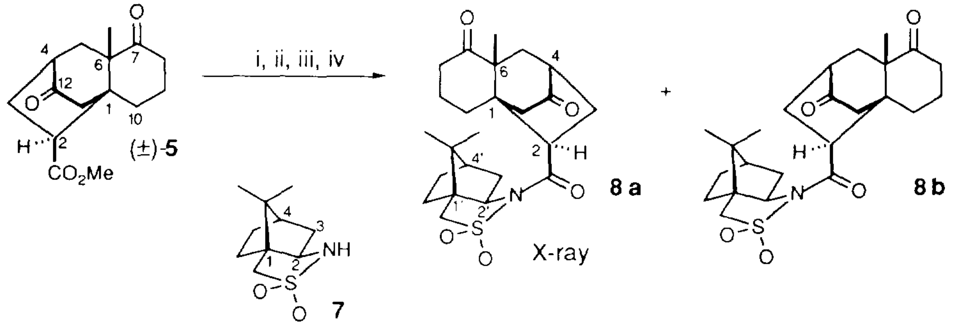


Reagents and conditions: i, LDA, THF, 0 °C; ii, methyl acrylate, 0 °C to room temperature.

X-Ray structure analysis was then carried out. Since the ester (±)-**5** was obtained as amorphous solid, we applied the following camphorsultam amide method.[6] One of the authors recently reported that (1*S*,2*R*,4*R*)-(−)-camphor sultam **7** was a very useful chiral auxiliary for optical resolution by HPLC and also for X-ray crystallographic determination of the absolute configuration of carboxylic acids. The camphorsultam amide method has the following advantages; i) a diastereomeric mixture of camphorsultam amides is easily separable by HPLC on silica gel; ii) camphorsultam amides generally crystallize as large prismatic crystals;

iii) the absolute configurations of the amides obtained can be determined by the X-ray Bijvoet method and also by the internal reference method using the camphor part with known absolute configuration.

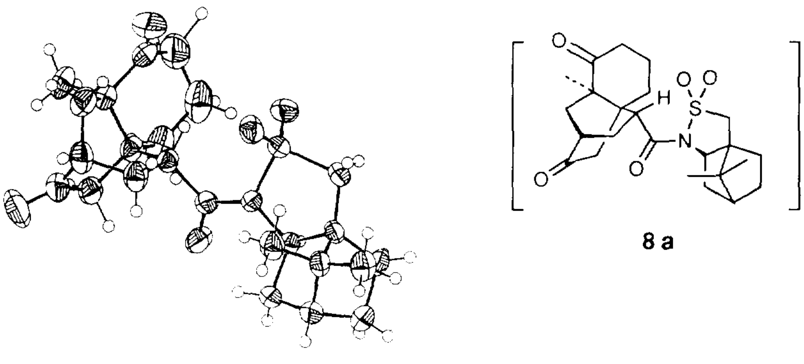
Scheme 2



Reagents and conditions: i, aq NaOH, EtOH, reflux; ii, $SOCl_2$, room temperature; iii, NaH, benzene, *d*-camphorsultam **7**, room temperature; iv, resolution by medium pressure LC.

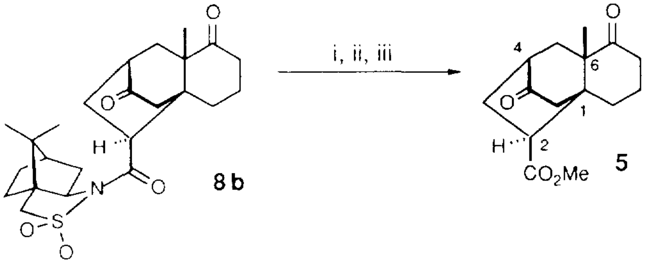
The ester (±)-**5** was hydrolyzed to give carboxylic acid which was then converted to acid chloride (Scheme 2). The reaction of the acid chloride obtained with the anion of **7** afforded a diastereomeric mixture of sultamamides **8a** and **8b**, which was easily separable by medium pressure LC (MPLC) on silica gel (hexane/EtOAc 1:1). Less polar diastereomer **8a** was recrystalized to give colorless prisms which were subjected to X-ray crystallography. The crystals were found to be monoclinic and the space group to be $P2_1$. As illustrated in Figure 1, amide **8a** has a skeleton of tricyclo[6.2.2.0^{1,6}]dodecan-7,12-dione, which indicates that the double Michael reaction proceeds *via* path b shown in Scheme 1. The absolute stereochemistry of **8a** was determined to be (1*R*,2*R*,4*S*,6*R*,1'*S*,2'*R*,4'*R*) by the anomalous dispersion effect of sulfur atom. The absolute configuration determined was confirmed by the internal reference method using the camphor part.

Figure 1



The more polar diastereomer **8b** was converted into ester (1*S*,2*S*,4*R*,6*S*)-**5** (Scheme 3). The sultamamide **8b** was reduced with lithium aluminiumhydride (LAH) to give in 75 % yield triol which was oxidized with Jones reagent. Esterification of the resulting keto-acid with diazomethane furnished in 38 % yield (1*S*,2*S*,4*R*,6*S*)-**5** which exhibited weak but distinct Cotton effects in the CD spectrum: λ_{ext} 304 nm, $\Delta\varepsilon$ −1.11, 294 nm, $\Delta\varepsilon$ −1.13 and 216 nm, $\Delta\varepsilon$ +1.67. Since the absolute configuration of the less polar diastereomer **8a** was determined by X-ray crystallography, the absolute configuration of [CD(−)304]-**5**[7] was established to be (1*S*,2*S*,4*R*,6*S*).

Scheme 3



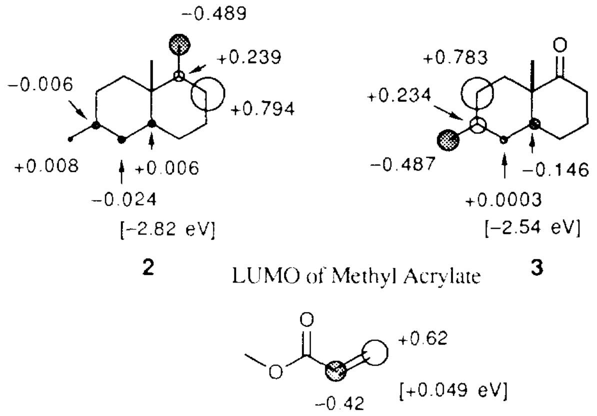
Reagents and conditions: i, LAH, THF; ii, Jones reagent, acetone, 0 °C; iii, diazomethane, Et_2O.

In order to get insight on the reaction pathway, semiempirical molecular orbital calculation by MOPAC[8] was carried out employing AM1 Hamiltonian in precise mode and revealed the preferential formation of the ester (±)-**5** rather than the ester (±)-**4**. *S*-cis conformation was chosen for methyl acrylate from observed relative stereochemistry of the ester **5**.

Calculated heat of formation of $\Delta^{1,2}$-enolate **2** ($\Delta_f H^\circ$ −90.38 kcal mol^{-1}) and the $\Delta^{6,7}$-enolate **3** ($\Delta_f H^\circ$ −84.79 kcal mol^{-1}) indicated that the $\Delta^{1,2}$-enolate **2** was thermodynamically more stable (more than 99.9% population) providing that effect of solvation was same in both enolates **2** and **3**. Actually, only $\Delta^{1,2}$-enolate **2** was trapped by us in 30% yield as silylenol ether[3] whose structure was apparent from its carbonyl absorption (ν 1671 cm^{-1}) in IR spectrum. On the other hand, the smallest atomic orbital electron population of the 7*S**-H among other protons α to carbonyl groups alluded kinetic generation of the enolate **3**.

Coefficients of HOMO of the $\Delta^{6,7}$-enolate **3** at both reacting termini, C-7 and C-4a, were +0.783 and −0.146, respectively as shown in Figure 2. On the other hand, HOMO of the $\Delta^{1,2}$-enolate **2** exhibited coefficients of +0.793 and +0.006 at C-2 and C-4a, respectively. Providing that the second Michael addition occurred concurrently (difference between double Michael *vs* anion accelerated Diels-Alder reaction is subtle[1]), these results indicated that the present double Michael reaction proceeded from the $\Delta^{6,7}$-enolate **3**, because the coefficient at C-4a of the $\Delta^{1,2}$-enolate **2** was too small and moreover the sign of the coefficient at C-4a was opposite to correlate with α-carbon of LUMO of methyl acrylate . Smaller energy gap between HOMO of the $\Delta^{6,7}$-enolate **3** and LUMO of methyl acrylate (ΔE 2.59 eV) than that of the $\Delta^{1,2}$-enolate **2** (ΔE 2.87 eV) would also favor annulation from the $\Delta^{6,7}$-enolate **3**. Though the $\Delta^{1,2}$-enolate **2** was trapped by C- or O-alkylation as noted in the work of Grieco *et al.*,[3] mode of present annulation *via* path b to give the ester **5** was understood by frontier orbital theory.

Figure 2


HOMO of Enolates **2** and **3**

LUMO of Methyl Acrylate

Stereochemical course of the present reaction was explained by chelation control. Methyl acrylate approached to the $\Delta^{6,7}$-enolate **3** from less hindered α-face. After taking *S*-cis conformation by chelation of oxygen of ester carbonyl of methyl acrylate with Li cation on the $\Delta^{6,7}$-enolate **3**, the double Michael reaction proceeded concurrently to afford the ester **5** .

In summary, we have shown that the double Michael reaction of Wieland-Miescher ketone **1** with methyl acrylate have proceeded from the $\Delta^{6,7}$-enolate **3** *via* path b to give the tricyclic ester **5** in symmetry allowed manner.

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Experimental

All m.p.s were determined with a Mitamura Riken hot-stage apparatus and were uncorrected. IR spectra were recorded on a JASCO FT/IR-8300 spectrophotometer for solutions in chloroform. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with JEOL-FX 90Q (90 MHz) or Bruker MSL-300 (300 MHz) instrument with tetramethylsilane as internal standard. Mass spectra were run on a JEOL JMS-DX300 spectrometer with a JMA-3500 data system. Circular dichroic spectrum was measured on a JASCO J-400X spectrophotometer. Ultraviolet spectrum was obtained on a JASCO Ubest-50 spectrophotometer. MPLC was carried out on a JASCO PRC-50 instrument with a silica gel packed column. Anhydrous sodium sulfate was used for drying organic extracts. THF was distilled from benzophenone ketyl before use.

Methyl (1S*,2S*,4R*,6S*)-6-*Methyltricyclo*[6.2.2.0^{1,6}]*dodecan*-7,12-*dion*-2-*carboxylate* **5**.— To a stirred solution of LDA, prepared from diisopropylamine (0.182 cm^3, 1.3 mmol) and butyllithium (0.74 cm^3, 1.65 mol dm^3 in hexane, 1.2 mmol) in THF (1 cm^3), was added racemic Wieland-Miescher ketone **1** (175 mg, 1 mmol) in THF (2 cm^3) at 0 °C. The resulting solution became black and curdy. After being stirred for 20 min, methyl acrylate (0.15 cm^3, 1.67 mmol) was added and stirring was continued overnight warming gradually to room temperature. The reaction was quenched by addition of aq. ammonium chloride and the product was extracted with ethyl acetate twice. Combined organic layers were washed with brine and evaporated to dryness *in vacuo*. The residue was purified by MPLC [eluent hexane:ethyl acetate (1:1)] to give the tricyclic ester **5** (74.4 mg, 28%); ν_{max}/cm^{-1} 3027, 2955, 1728, 1456, 1438, 1231, 1198, and 1173; δ(300 MHz) 1.18 (3 H, s, Me), 1.35 (1H, ddd, *J* 14.2, 4.3 and 2.9 Hz), 1.5 (1H, d, *J* 13 Hz), 1.85—2.15 (5H, m), 2.21 (1H, dd, *J* 19 and 2.2 Hz), 2.36 (1H, dm, *J* 14 Hz), 2.43 (1H, m), 2.7 (2H, m), 2.79 (1H, dd, *J* 14.3 and 2 Hz), 3.01 (1H, d, *J* 19 Hz) and 3.7 (3H, s); *m/z* 265 (M$^+$ + 1, 3%), 264 (M$^+$, 16), 178 (56), 163 (69), 160 (100), 145 (21) 121 (18) and 55 (19) (Found:M$^+$, 264.1359. $C_{15}H_{20}O_4$ requires *m/z* , 264.13615).

(1R*,2R*,4S*,6R*)-6-*Methyltricyclo*[6.2.2.0^{1,6}]*dodecan*-7,12-*dion*-2-*carboxamide* *N*-(1'S,2'R,4'R)-*camphorsultam* **8a** and **8b**.—A solution of the tricyclic ester **5** (61.7 mg, 0.234 mmol) in aq. sodium hydroxide (1 cm^3, 1 mol dm^{-3}) and ethanol (3 cm^3) was heated under reflux for 1.5 h under nitrogen. After being cooled to room temperature, hydrochloric acid (1 mol dm^{-3}) was added. The product was extracted with ethyl acetate twice and combined organic layers were washed with brine. Evaporation of the extract afforded fine crystals of (1R*,2R*,4S*,6R*)-6-*methyltricyclo*[6.2.2.0^{1,6}]*dodecan*-7,12-*dion*-2-*carboxylic acid* (55.5 mg, 95%) ; ν_{max}/cm^{-1} 2956, 1708, 1466, 1456, 1409, 1322, 1235, 1186 and 909; δ (90 MHz) 1.19 (3 H, Me), 1.1—3.1 (14 H, m) and 8.1 (1 H, br, CO_2H); *m/z* 251 (M$^+$ +1 , 8%), 250 (M$^+$, 40), 178 (64), 163 (78), 160 (100), 145 (35) and 55 (40) (Found:M$^+$, 250.12034. $C_{14}H_{18}O_4$ requires *m/z* , 250.1205).

A solution of the acid (37.2 mg, 0.15 mmol) in thionyl chloride (0.5 cm^3) was stirred at room temperature for 1 h. Excess thionyl chloride was evaporated *in vacuo* and the residue was used for further reaction without purification.

To a stirred suspension of sodium hydride (14 mg, 60%, 0.3 mmol) in benzene (0.5 cm^3) was added crystals of *d*-camphorsultam (64.9 mg, 0.3 mmol) at room temperature under nitrogen. After being stirred for 1 h, a solution of acid chloride in benzene (2 cm^3) was added at 0 °C and the resulting solution was stirred at room temperature for 3 h. The reaction was quenched by addition of water followed by hydrochloric acid (1 mol dm^{-3}). The product was extracted with chloroform three times. Organic layers were washed with brine. Evaporation of the extract followed by MPLC separation [eluent hexane:ethyl acetate (1:1)] provided recovered *d*-camphorsultam (45.3 mg), less polar diastereomer **8a** (10.1 mg, 15%) and more polar diastereomer **8b** (18.6 mg, 28%). Less polar diastereomer **8a** had; m.p. 250 °C (decomposition); ν_{max}/cm^{-1} 2964, 2359, 2342, 1708, 1455, 1414, 1338, 1265, 1237, 1166 and 1133; δ (300 MHz) 0.94 (3 H, s, Me), 1.09 (3 H, s, Me), 1.15 (3 H, s, Me), 1.2—1.5(4H, m), 1.5—1.75 (4H, m), 1.8—2.15 (10H, m), 2.84 (1H, d, *J* 14.3 Hz), 3.03 (1H, t, *J* 8.9 Hz), 3.32 (1H, d, *J* 19.3 Hz), 3.43 (1H, d, *J* 13.8 Hz), 3.51 (1H, d, *J* 13.8 Hz) and 3.87 (1H, t, *J* 6.5 Hz) ; *m/z* 448 (M$^+$ + 1, 8%), 447 (M$^+$, 23), 270 (38), 232 (41), 204 (46), 161 (52), 160 (100), 136 (30), 135 (60), 121 (32), 93 (35) and 55 (53) (Found:M$^+$, 447.20767. $C_{24}H_{33}O_5NS$ requires M, 447.20793). More polar diastereomer **8b** was recrystalized from chloroform and hexane; mp. 220—240 °C; ν_{max}/cm^{-1} 2964, 2359, 2343, 1712, 1456, 1413, 1338, 1264, 1236, and 1133; δ (90 MHz) 0.98 (3 H, s, Me), 1.14 (6 H, br s, Me x 2) and 1.0—3.0 (24 H, m); *m/z* 448 (M^+ + 1, 7%), 447 (M^+, 23), 232 (43), 204 (56), 178 (33), 163 (96), 162 (27), 160 (100), 135 (47) and 55 (44) (Found:M^+, 447.20776. $C_{24}H_{33}O_5NS$ requires M, 447.20793).

X-ray Crystal Structure Determination of Amide **8a**.–Single crystals were obtained as colorless prisms by recrystalization of amide **8a** from chloroform/hexane. A crystal (dimension 0.30 × 0.23 × 0.08 mm) was selected for data collection and mounted on a Rigaku AFC-6B automated four circle diffractometer. The crystal was found to be monoclinic, and the unit cell parameters and orientation matrix were obtained. Data collection was carried out by using a $2\theta-\theta$ scan: formula, $C_{24}H_{33}NO_5S$; formula weight, 447.60; space group $P2_1$; a = 13.888 (2) Å, b = 6.9646 (5) Å, c = 11.496 (2) Å, β = 90.46 (1)°, vol = 1111.9 (2) Å^3; Z = 2; ρ(calcd) = 1.337 g/cm^3; ρ(obsd) = 1.340 g/cm^3 (by flotation using a CCl_4-hexane solution); radiation, Cu K_α (1.54178 Å); monochrometor, graphite crystal; linear absorption coefficient, 14.84 cm^{-1}; temperature, 20 °C; scan type, $2\theta-\theta$; scan speed, 2.0°/minute; scan range, 1.3° + 0.3° tan θ; 2θ scan limits, 2-130°; standard reflections, 3 per 50 reflections; indices, (0,1,1), (−3,0,2), (2,0,1); crystal stability, no indication of standard reflection decay during data collection; total reflections scanned, 2163; unique data $F_o > 3.0\ \sigma(F_o)$, 1910.

The position of the most non-hydrogen atoms were found by the direct method, and then those of the remaining non-hydrogen atoms were found by successive Fourier syntheses. All hydrogen atoms were found by the difference Fourier syntheses. Full matrix least-squares refinement of positional parameters and anisotropic thermal parameters for non-hydrogen atoms, including anomalous scattering factors of sulfur, oxygen, nitrogen and carbon atoms, led to the final convergence with R = 0.0402 and R_w = 0.0440 (final no. of variables, 379) for the (1*R*,2*R*,4*S*,6*R*,1′*S*,2′*R*,4′*R*) absolute configuration, while a similar calculation for the mirror image structure gave R = 0.0414 and R_w = 0.0457. In the full matrix least-squares calculation, the isotropic thermal parameters of hydrogen atoms were not included as variables in the refinement, but calculated from the thermal parameters of the non-hydrogen atoms to which the hydrogen atoms were attached. The absolute configuration of the sultam amide of **8a** was determined as illustrated in Figure 1 and formula **8a**. The (1*R*,2*R*,4*S*,6*S*) absolute configuration of the diketo-carboxylic part was also assigned by using the (1′*S*,2′*R*,4′*R*)-(−)-2,10-camphorsultam part as an internal reference of the absolute configuration. The lists of atomic parameters, bond lengths and bond angles of **8a** are deposited at the Cambridge Crystallographic Data Center. The list of observed and calculated structure factors may be obtained from one of the authors (N.H.) upon request.

Methyl (1S,2S,4R,6S)-6-*Methyltricyclo*[6.2.2.$0^{1,6}$]*dodecan*-7,12-*dion*-2-*carboxylate* **5**.— More polar diastereomer of the sultam amide **8b** (63 mg, 0.14 mmol) in THF (5 cm^3) was added LAH (40 mg, 1.08 mmol) at 0 °C under nitrogen. After being stirred for 1 h at room temperature, the reaction was quenched by addition of aq. ammonium chloride. Usual work up followed by flash chromatography gave triol (25.2 mg, 75%).

To a stirred solution of the triol (25.2 mg, 0.105 mmol) in acetone (4 cm^3) was added Jones reagent dropwise at 0 °C. After being stirred for 30 min, the product was extracted with ethyl acetate twice. Organic layers were treated with ethereal solution of diazomethane. Evaporation of the mixture followed by repeated (twice) MPLC purification of the residue afforded the tricyclic ester **5** (10.6 mg, 38%) which crystallized spontaneously (m.p. 113.5–114.5 °C); UV (EtOH) λ_{max} 295.6 (ε 60) and 200 nm (ε 1,000, end absorption); CD (EtOH) λ_{ext} 304 ($\Delta\varepsilon$ −1.11), 294 ($\Delta\varepsilon$ −1.13) and 216 nm ($\Delta\varepsilon$ +1.67).

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8. AM1 calculation was carried out with Apple Macintosh [MOPAC Ver. 6.00, Stewart, J. J. *QCPE Bull.* **1990**, *10*(4), 86].

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