Diastereoselective Synthesis of a Simplified Analogue of Artemisinin with a Substituted Ring Junction

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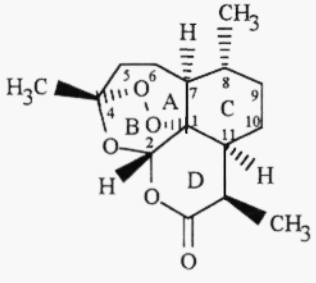
Abstract: A tricyclic 1,2,4-trioxane was synthesised in a diastereoselective way via a photooxygenation of an enol ether readily derived from a chiral β-ketoester in four steps.

Introduction

Artemisinin 1 is the active principle isolated from the *Qinghao* (*Artemisia annua L.*(1)), which was used to treat malaria in traditional chinese herbal medicine. Important biological activities displayed by artemisinin and its analogues have stimulated the development of synthetic strategies for the preparation of this class of sesquiterpene endoperoxides (2). Numerous modifications of artemisinin have been made, principally on the lactone ring, in order to increase biological activity against drug resistant forms of malaria, notably *Plasmodium falciparum*. Examination of the structure-activity relationship suggests that the 1,2,4-trioxane system is essential, whereas the lactone ring is not crucial (1a,3). Curiously, no angular substitution at the A-C ring junction has ever been undertaken.



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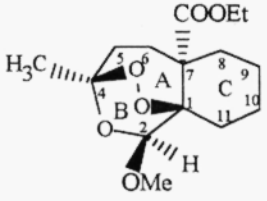

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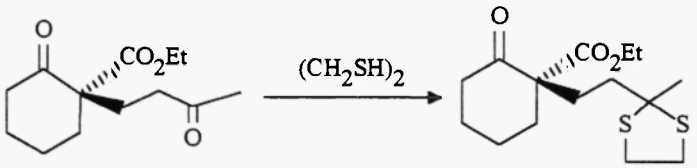
Results and Discussion

We report the synthesis of such a tricyclic artemisinin analogue 2 where the C-7 ring junction is quaternized with an ester group. Moreover, introduction of a polar group, easily convertible, could increase solubility (artemisinin is essentially water insoluble) and bioavailability of this type of compound.

Chirality was introduced by a Michael addition of methyl vinyl ketone on an optically active β-enaminoester, followed by acetic acid hydrolysis (4). The β-ketoester 3 thus obtained, in agreement with a previous report (5), was selectively protected with 1,2-ethanedithiol and catalytic amounts of BF_3-OEt_2 (less than 15% of bisprotected product was obtained and could be recycled). The next step consisted of a Wittig olefination with methoxymethyltriphenylphosphonium chloride to prepare an enol ether necessary for the construction of the 1,2,4-trioxane system.

Our attention was mainly focused on the latter reaction that implicated a sterically hindered and enolizable ketone. Recently (6), some difficulties were described in Wittig homologation on a similar compound where a methyl group substituted for an angular ethyl ester. By the use of several bases (NaH, KH, BuLi, KO-*t*-Bu,...) and different experimental conditions we were unable to prepare the desired products. Yields were poor and, at best, a large amount of starting material was recovered. Fortunately, by using a large excess of potassium bistrimethylsilylamide in THF, we could prepare *E* and *Z* vinyl ethers 5 respectively in a 86:14 ratio.

Each structure was definitely established by ^1H, ^{13}C, HMBC, HMQC and NOE NMR spectroscopy after chromatographic separation on silica gel. All chemical shifts are in agreement with those reported by Jefford (7) on similar compounds.



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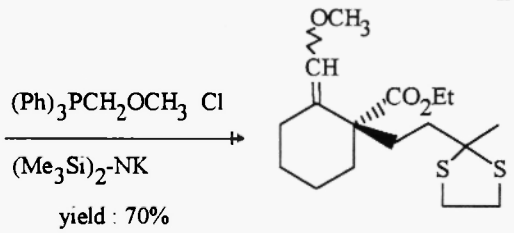


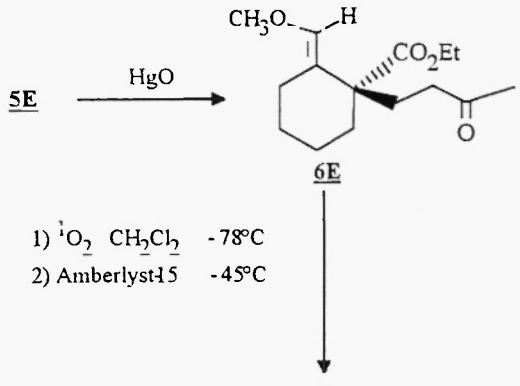
yield : 70%

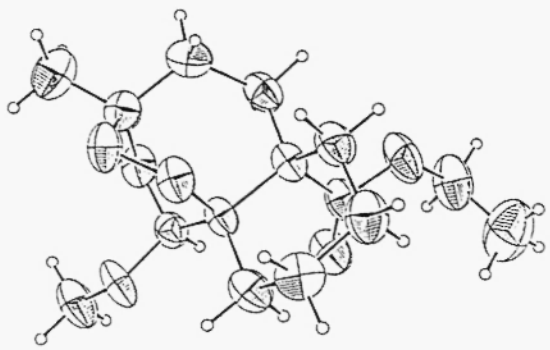
5 **E/Z : 86/14**

We assume that formation of the thermodynamic 5*E* isomer is explained by stabilisation of the oxyphosphonium form with the ethoxycarbonyl group. Addition of lithium salts during the reaction did not change the *E*/*Z* ratio.

The 5*Z* isomer was not very stable and deprotection of the keto group (which led to a more unstable compound) followed by photooxygenation did not permit us to prepare a 1,2,4-trioxane derivative.

On the other hand, the 5*E* isomer could be cleanly deprotected by HgO and the action of singlet oxygen (generated by methylene blue, O_2, halogen lamp) on 6*E* followed by acidic hydrolysis using a large excess of Amberlyst-15 led to a single (-) - "endo"-methoxy-1,2,4 trioxane 2 (40%).





X- Ray structure of 2

NOEs between H_2, H_{9ax} and CH_2 of the ester group permitted us to establish the structure of 2. In order to confirm this structure, corresponding racemate 2, which was available in greater amounts, was studied by X-ray diffraction. The synthetic work is pursued in our laboratory in order to prepare other functional groups on the C-7 centre. Biological studies, in particular comparisons between racemic and enantiomeric 1,2,4-trioxanes are in progress.

Experimental

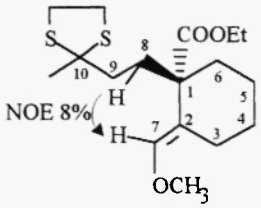
Thin layer chromatography was performed on Kieselgel 60 F Merck or Riedel-DeHaen. Flash chromatography was done with Merck 9385 40-63 mm or Riedel-DeHaen 31607 silica gel. Elemental analysis was performed on a Perkin Elmer 240 apparatus. ^{1}H NMR spectra were recorded on a Bruker AC 200 P (200 MHz or 400 MHz) and tetramethylsilane (TMS) was used as internal reference. Chemical shifts were expressed in ppm and coupling constants in Hz.

Ethyl (S)-1-[3-(1,3-Dithiolan-2-yl)butyl]-2-oxo-cyclohexane-1-carboxylate 4: A solution of 3 (2.40 g ; 10 mmol) , BF_3-Et_2O (0.5 ml) and 1,2 ethanedithiol (0.94 g ; 10 mmol) in 75 ml of acetic acid was stirred at 60 °C for 2 h. Excess of acetic acid was evaporated under reduced pressure and the resulting residue was dissolved in Et_2O and washed with saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried and concentrated under reduced pressure affording a mixture of mono and bisprotected ketones which was chromatographed on silica gel (petroleum ether: AcOEt = 90:10) to give 4 (2.31 g, 73%). (ee = 81%) : $[\alpha_D]^{20}$ = - 56.6 (c = 0.53; CCl_4). ^{1}H NMR (C_6D_6, 200 MHz) δ: 4.00-3.80 (q, 2H, O-CH_2, J=7 Hz), 2.85 (s, 4H, CH_2-S), 2;40-2.20 (m, 4H), 2.15-1.85 (m, 3H), 1.70 (s, 3H, CH_3-C-S), 1.60-1.10 (m, 5H), 0.85 (t, 3H, CH_3-CH_2, J=7 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 206.0, 171.7, 66.9, 61.0, 60.6, 41.2, 40.3, 40.1 (2), 40.0, 36.1, 32.6, 27.6, 22.7, 14.2.

Ethyl (S)-1-[3-(1,3-dithiolan-2-yl)butyl]-2-(methoxymethylidene)cyclohexane-1-carboxylate 5: To a cold solution (0 °C) of methoxymethyltriphenylphosphonium chloride (1.71 g ; 5 mmol) in 10 ml of dry THF was added dropwise 10 ml (5 mmol) of a 0.5 M solution of potassium bistrimethylsilylamide in toluene under argon. After 1 h, 4 (316 mg ; 1 mmol) in 2 ml of THF was added and the solution was stirred at room temperature for 12 h. The mixture was then poured into water, extracted with Et_2O and the extract was dried over Na_2SO_4. The organic layer was concentrated under reduced pressure to afford a mixture of **5E** and **5Z** isomers which was chromatographied on a silica gel column (petroleum ether : AcOEt = 95:5) to finally give **5E** (205 mg, 60%) and **5Z** (36 mg, 10%). **5E**: $[\alpha_D]^{20}$ = - 67 (c = 0.5; CCl_4). ^{1}H NMR (CD_3OD, 400 MHz) δ: 6.15 (s, $1H_7$), 4.00 (m, 2H, CH_2-O), 3.18 (s, 3H, CH_3-O), 2.98 (ddd, $1H_{3e}$, JH_{3e},H_{3ax} = 13 Hz, JH_{3e},H_{4ax} = 4 Hz, JH_{3e},H_{4e} = 4 Hz), 2.80 (bs,4H, CH_2-S), 2.39 (ddd, $1H_{6e}$, JH_{6e},

H_{6ax} = 13 Hz, JH_{6e}, H_{5ax} = 5 Hz, JH_{6e}, H_{5e} = 5 Hz), 2.30 (ddd, $1H_8$, JH_8,H_8' = 12 Hz, JH_8,H_9 = 12 Hz, JH_8, $H_{9'}$ = 3 Hz), 2.18 (ddd, $1H_9$, JH_9,$H_{9'}$ = 12 Hz, JH_9, H_8 = 12 Hz, JH_9,H_8' = 3 Hz), 2.08 (m, $1H_{3ax}$), 2.07 (m, $1H_{8'}$), 2.06 (m, $1H_9$), 1.80 (s, 3H, CH_3-C_{10}), 1.75 (m, $1H_{5ax}$), 1.64 (m, $1H_{4e}$), 1.62 (m, $1H_{5e}$), 1.37 (m, $1H_{4ax}$), 1.32 (m, $1H_{6ax}$), 0.98 (t, 3H, CH_3-CH_2, J =7 Hz). ^{13}C NMR (C_6D_6, 100 MHz) δ: 175.5 (C=O), 142.2 (C_7), 119.2 (C_2), 67.2 (C_{10}), 60.3 (CH_2-O), 59.0 (CH_3-O), 51.1 (C_1), 40.5 (C_9), 40.0 (CH_2-S), 35.9 (C_6), 33.7 (C_8), 32.6 (CH_3-C_{10}), 27.1(C_4), 24.1 (C_3), 23.6 (C_5), 14.4 (CH_3-CH_2).

5Z (ee = 81%) : $[\alpha_D]^{20}$ = +42 (c = 0.66; CCl_4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.77 (s, $1H_7$), 4.18-4.08 (m, 2H, CH_2-O), 3.42 (s, 3H, CH_3-O), 3.32 (m, 4H, CH_2-S), 2.14 (ddd, $1H_9$, JH_9,$H_{9'}$ = 11 Hz, JH_9, H_8 = 11 Hz, JH_9,H_8' = 5 Hz), 1.96 (m, $4H_{6,3}$), 1.95 (m, $1H_8$), 1.79 (m, $1H_9$), 1.78 (s, 3H, CH_3-C_{10}), 1.65 (m, $1H_4$), 1.59 (m, $2H_3$), 1.50 (m, $1H_{8'}$), 1.35 (m,$1H_4$), 1.26 (t, 3H, CH_3-CH_2, J = 7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 176.9 (C=O), 140.9 (C_7), 116.0 (C_2), 67.1 (C_{10}), 60.1 (CH_2-O), 59.1 (CH_3-O), 48.5 (C_1), 39.9 (C_9), 39.5 (CH_2-S), 34.8 (C_8), 32.5 (CH_3-C_{10}), 30.7 (C_3 or C_6), 27.8 (C_6 or C_3), 26.4 (C_4), 21.7 (C_5), 14.1 (CH_3-CH_2).



5E

Ethyl (E)-(S)-1-(3-oxobutyl)-2-(methoxymethylidene)cyclohexane-1-carboxylate 6: A solution 0.63 g (2.9 mmol) of HgO in 4 ml of (CH_3CN/H_2O : 85/15) was stirred for 0.5 h with 0.05 ml of BF_3-Et_2O. A solution of 0.2g (0.58 mmol) of **5E** in 1ml of CH_3CN was added to this mixture and the whole was stirred at room temperature for 10 min. Excess of HgO was removed by filtration over celite and washed with Et_2O. The organic layer obtained was neutralised with a saturated aqueous $KHCO_3$, washed with brine, then dried and concentrated under reduced pressure. The pale yellow oil obtained was purified over a silica gel column (petroleum ether : AcOEt = 90:10) to give **6E** (150 mg, 85%). **6E** : $[\alpha_D]^{20}$ = -12.1 (c = 0.33; CCl_4). ^{1}H NMR (CH_3OD, 200 MHz) δ: 5.85 (s, 1H), 4.10 (t, 2H, O-CH_2, J=7 Hz), 3.55 (s, 3H, CH_3-O), 2.70-2.30 (m, 3H), 2.20-2.00 (m, 2H), 2.15 (s, 3H, CH_3CO), 1.90-1.40 (m, 5H), 1.30-1.10 (m, 2H), 1.20 (t, 3H, CH_3-CH_2, J=7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 208.1, 175.1, 141.5, 118.9, 60.4, 59.5, 49.3, 38.8, 35.2, 30.0, 28.7, 26.4, 23.3, 22.9, 14.2.

Ethyl (1R,2S,4R,7S)-1,4-Epidioxy-2-methoxy-4-methyl-3-oxabicyclo[5.4.0]-undecane-7-carboxylate 2: A solution of **6E** (400 mg ; 1.5 mmol) and Methylene Blue (2 mg) in dry CH_2Cl_2 was photooxygenated at -78 °C for 5 h. Amberlyst-15 (1 g) was added with stirring for a night at -45°C. Amberlyst-15 was removed by filtration over celite and CH_2Cl_2 was evaporated. The residue was purified by flash chromatography column (petroleum ether : AcOEt = 95:5) to give **2** (180 mg, 40%) which was crystallised from pentane. **2** : $[\alpha_D]^{20}$ = -32 (c = 0.49; CCl_4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.50 (s, $1H_2$), 4.15 (q, 2H, O-CH_2, J = 7 Hz), 3.50 (s, 3H, O-CH_3), 2.43 (ddd, $1H_{5ax}$, JH_{5ax}, H_{5e} = 14 Hz, JH_{5ax}, H_{6ax} = 14 Hz, JH_{5ax}, H_{6e} = 5 Hz), 2.15 (m, $1H_{11e}$), 2.09 (m, $1H_{6ax}$), 2.07 (m, $1H_{8ax}$), 1.92 (ddd, $1H_{5e}$, JH_{5e}, H_{5ax} = 14 Hz, JH_{5e}, H_{6ax} = 5 Hz, JH_{5e}, H_{6e} = 4 Hz), 1.79 (m, $1H_{11ax}$), 1.74 (m, $1H_{8e}$), 1.60 (m, $1H_{6e}$), 1.55 (m, $1H_{9e}$), 1.51-1.41 (m, $2H_{10}$), 1.39 (s, 3H, CH_3-C_4), 1.25 (t, 3H, CH_3-CH_2, J = 7 Hz), 1.15 (m, $1H_{9ax}$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 175.6 (C=O), 102.9 (C_4), 98.2 (C_2), 83.0 (C_1), 60.5 (CH_2-O), 55.6 (CH_3-O), 52.0 (C_7), 34.8 (C_5), 32.2 (C_6), 31.1 (C_8), 30.0 (C_{11}), 25.8 (CH_3-C_4), 22.7 (C_9), 19.5 (C_{10}), 14.1 (CH_3-CH_2). *Anal.* Calcd for $C_{15}H_{24}O_6$: C, 60.00; H, 8.00. Found: C, 60.09; H, 8.10.

45 mg (12%) of the formylcyclohexene derived from the "ene" reaction and 54 mg (15%) of **3** were also isolated.

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