Total Synthesis of Sollasin a and Sollasin d via Photocycloaddition of Methyl 2,4-Dioxopentanoate to Methyl *E*-2-Methyl-2-butenoate

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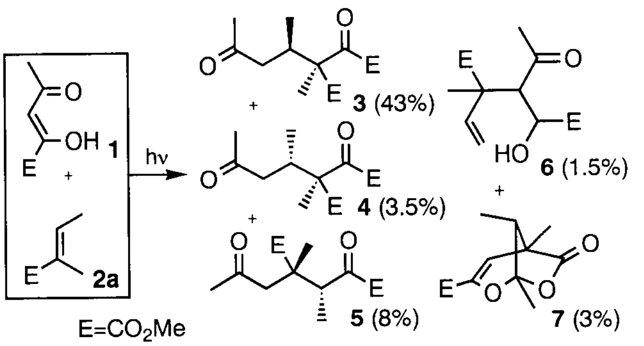
Starting from photocycloaddition of methyl 2,4-dioxopentanoate to methyl tiglate, an electron-deficient olefin, methyl-migrated monocyclofarnesyl sesquiterpenoids, *d,l*-sollasin a and d, antibacterial compounds, were synthesized.

Methyl 2,4-dioxopentanoate (**1**) is a versatile C_5 photosynthon to obtain homologous isoprenoids;[1] *e.g.*, iridanes from **1** and isoprene,[2] cyclonerodanes from **1** and myrcene.[3] Particularly, its usefulness has been verified by the reactions with conjugated olefins[2-5] or by easy furnishment of five-membered carbocycles[6,7] in high regioselectivity. However, the photocycloadditions examined have been limited to that with olefins having electron-donating substituents, such as cycloalkenes,[8] alkyl- and alkoxyethenes,[9] and arylethenes.[10] Therefore, it is worthy of investigating the reactivity and regioselectivity of the photochemical reaction of **1** with an electron-deficient olefin, methyl *E*-2-methyl-2-butenoate (methyl tiglate, **2a**).

Irradiation of a benzene solution **1** and **2a** in a quartz vessel under nitrogen atmosphere for 3 h afforded, after silica-gel chromatography, five photoproducts (**3**, 43%, **4**, 3.5%, **5**, 8%, **6**, 1.5%, and **7**, 3%). Among them, **3**, **4**, and **5** were *retro*-aldolized [2+2] cycloadducts; **3** and **4** were diastereomers each other, and **5** was their regioisomer.

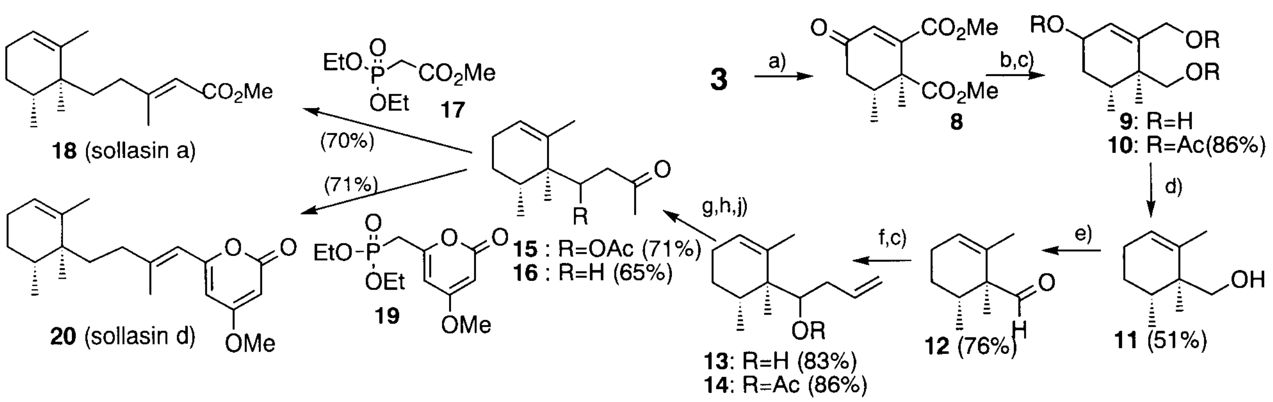


Scheme 1.

In the ^1H NMR spectra, **5** showed an *AB*-type pair of doublets, *J*=18 Hz, while **3** and **4** showed an each *ABX*-spin system. Therefore, their regiochemistry was assigned as depicted in Scheme 1. Assuming a retention of geometrical structure of **2a** during the reaction, the major product, **3**, was assigned as (3*R**,4*S**)-derivative, and **4**, as (3*R**,4*R**)-. This assignment was supported by NOE measurement. The structure of **3** suggested that the cycloaddition was controlled by not the electronic effect, but the stability of the delocalized diradical intermediate; *i.e.*, less-substituted site of the olefins formed a linkage to 3-position of **1**.[11]

This means that the tetrasubstituted cyclohexenone from the major product **3** could be employed for synthesis of methyl-migrated monocyclofarnesyl derivatives, *e.g.*, sollasin d, isolated from a marine sponge, *Poecillastra sollasi*,[12,13] as an antibacterial compounds against *Candida albicans* and *Cryptococcus neoformans*. Herein the total synthesis of sollasin d as well as sollasin a in the racemic form is described. Recently, Angers and Canonne synthesized sollasin a.[14]

The cyclization of **3** gave a desired cyclohexenone (**8**). Removal of the oxygen functions was then achieved *via* diisobutylaluminum hydride reduction of **8** to a triol (**9**), acetylation to a triacetate (**10**), Birch reduction (with lithium in liquid ammonia in the presence of 2-propanol) to a (1,2,6-trimethylcyclohex-2-enyl)methanol (**11**), and PDC-oxidation to an aldehyde (**12**). The Grignard reaction with allylmagnesium chloride of **12** gave a homoallyl alcohol (**13**), and the Wacker reaction[15] with its acetate



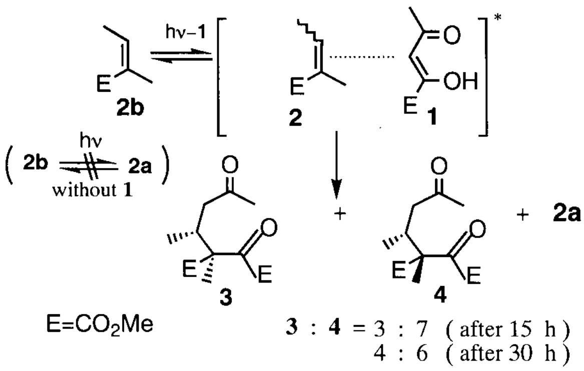
Reagents : a) TsOH/ benzene; b) DIBAH/ toluene; c) Ac_2O/ pyridine; d) Li/ liq. NH_3, *i*-PrOH; e) PDC/ CH_2Cl_2;f) $CH_2{=}CHCH_2MgCl$/ THF; g) O_2, CuCl, PdCl/ aq. DMF; h) TsOH/CH_2Cl_2; j) $(C_8H_{17})_3NMeCl$, $NaHCO_3$, $Na_2S_2O_4$.

Scheme 2.

(**14**) afforded a β-acetoxy ketone (**15**). Elimination and dithionite-reduction under phase-transfer conditions[16] of **15** afforded a common precursor (**16**).

The final step of the synthesis was accomplished by Wittig-Horner reaction;[17] *i.e.*, **16** was condensed at room temperature for 72 h with the anion prepared from methyl (diethoxyphosphoryl)acetate **17** to give sollasin a (**18**)[18] in 70% yield, and with the anion carrying α-pyrone chromophore (**19**) to give sollasin d (**20**) in 71% yield. The spectral data stated in literature[12] were identical within experimental error to our totally synthesized samples.

It is interesting to note that the irradiation of **1** with methyl *Z*-2-methyl-2-butenoate (methyl angelate, **2b**), afforded two common major products, **3** and **4** in different ratio; the ratio of **3**:**4** was 3:7 after 15 h, and 4:6 after 30 h, and furthermore, **2a** was detected in the recovered butenoate fractions. Irradiation of **2b** without adding **1** caused no photoisomerization. Consequently, the isomerizations between **2a** and **2b** should occur via an exciplex formation (**1**···**2**)*.



Scheme 3.

Finally, the present procedure will offer an applicability of **1** as a photosynthon to prepare sterically crowded alicyclics.

References and Notes

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18 The new compounds are fully characterized. Due to a limited space available, only the ^{1}H and ^{13}C NMR spectra of **18** and **20** in $CDCl_3$ are compiled. The discrepancies of the ^{13}C NMR chemical shifts from the figures cited in ref. 12 are shown in brackets.

18: δ(H)=0.86(3H, d, *J*=7.0 Hz), 0.87(3H, s), 1.46(2H, m), 1.52(2H, m), 1.60(3H, td, *J*=2.3, 1.1 Hz), 1.67(1H, m), 1.68(1H, m), 1.79(1H, m), 1.95(2H, m), 2.07(1H, m), 2.17(3H, d, *J*=1.1 Hz), 3.68(3H, s), 5.44(1H, br s), and 5.66(1H, qm, *J*=1.1 Hz); δ(C)=15.8(+0.1), 19.1(2C, ±0), 21.0(±0), 25.5(±0), 26.9(±0), 33.3(±0), 34.4(±0), 35.7 (±0), 40.4(-0.1), 50.8(±0), 114.6(±0), 124.7(±0), 139.0 (±0), 161.6(±0), and 167.3(±0).

20: δ(H)=0.88(3H, d, *J*=6.0 Hz), 0.89(3H, s), 1.45(2H, m), 1.54(2H, m), 1.61(3H, td, *J*=2.3, 1.1 Hz), 1.70(1H, m), 1.81(1H, m), 1.95(2H, m), 2.09(1H, m), 2.12(3H, brs), 3.80(3H, s), 5.41(1H, d, *J*=2.2 Hz), 5.45(1H, brs), 5.77(1H, brs), and 5.78(1H, d, *J*=2.2 Hz); δ(C)=15.8 (±0), 19.1(±0), 19.6(±0), 21.0(±0), 27.0 (+0.1), 25.5 (±0), 33.3 (±0), 34.7(±0), 36.5(±0), 40.5(±0), 55.7(±0), 87.4 (±0), 100.7(±0), 116.3(±0), 124.6(-0.1), 139.0(±0), 151.3(-0.1), 160.4(±0), 164.5(±0), and 171.4(±0).