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First total synthesis and determination of the absolute configuration of strictifolione, a new 6-(ω-phenylalkenyl)-5,6-dihydro-α-pyrone, isolated from *Cryptocarya strictifolia*

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Abstract—Starting from (*S*)-malic acid and (*S*)-glycidol, the first total synthesis of strictifolione, a new 6-(ω-phenylalkenyl)-5,6-dihydro-α-pyrone isolated from *Cryptocarya strictifolia*, was accomplished, which confirmed its structure including the absolute configuration of the asymmetric centers.

Recently, a number of 5,6-dihydro-α-pyrone derivatives possessing an ω-arylalkyl side chain at the C6 position have been isolated from the genus *Cryptocarya* (Lauraceae).[1] The biological activities of these compounds have not been well studied, but, some have been found to exhibit significant antifungal[1g] or cytotoxic[1a] activities. Their structures were elucidated mainly based on spectroscopic methods, and among them, the syntheses of cryptocaryalactone[2] and kurizilactone[3] have been reported so far. In the course of study on the chemical constituents of the *Cryptocarya* plants in Indonesia,[4] we have recently isolated a new 6-substituted 5,6-dihydro-α-pyrone (**1**),[5] named strictifolione, from *Cryptocarya strictifolia*, and proposed its structure based on spectroscopic analysis, as follows. The relative stereochemistry of the 1,3-diol function at C4′ and C6′ was elucidated from the ^{1}H NMR spectrum of the acetonide derivative (**4**), and the absolute configurations of their stereogenic centers were deduced by the Mosher method. The absolute configuration at C6 was assumed based on the Cotton effect in the CD spectrum. To confirm the structure inferred by spectroscopic analysis, we attempted the chiral total synthesis of **1**.

Our basic approach to strictifolione synthesis, which features the condensation of two fragments in the last stage of the synthesis, both of which can be prepared from chiral synthons (**2** and **3**) with known absolute stereochemistry, is outlined in Fig. 1.

Before starting the total synthesis, we prepared fragment **5** by degrading the natural product (Scheme 1) to confirm the absolute configuration of the 1,3-diol part in **1** by means of direct comparison with the synthetic intermediate described below. Thus, acetonide (**4**) prepared from natural **1** was treated with $NaIO_4$ in the presence of a catalytic amount of OsO_4 in aqueous

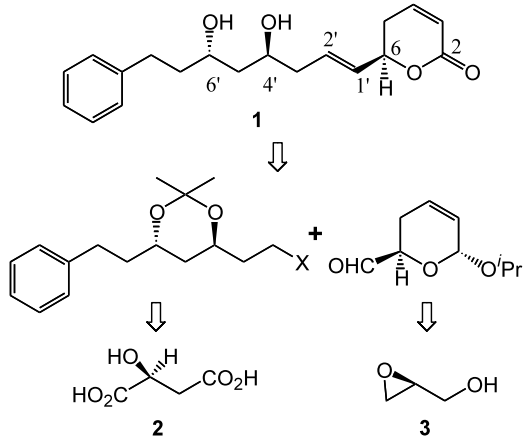

Figure 1.

Keywords: *Cryptocarya*; α-pyrone; chiral total synthesis; absolute configuration.

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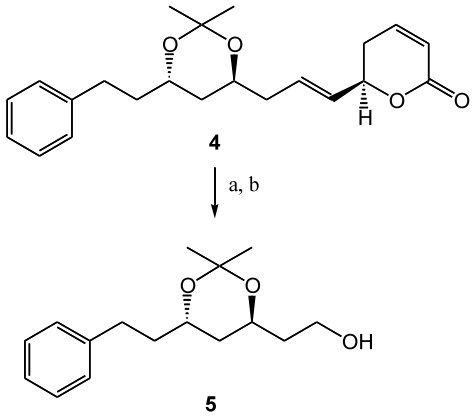
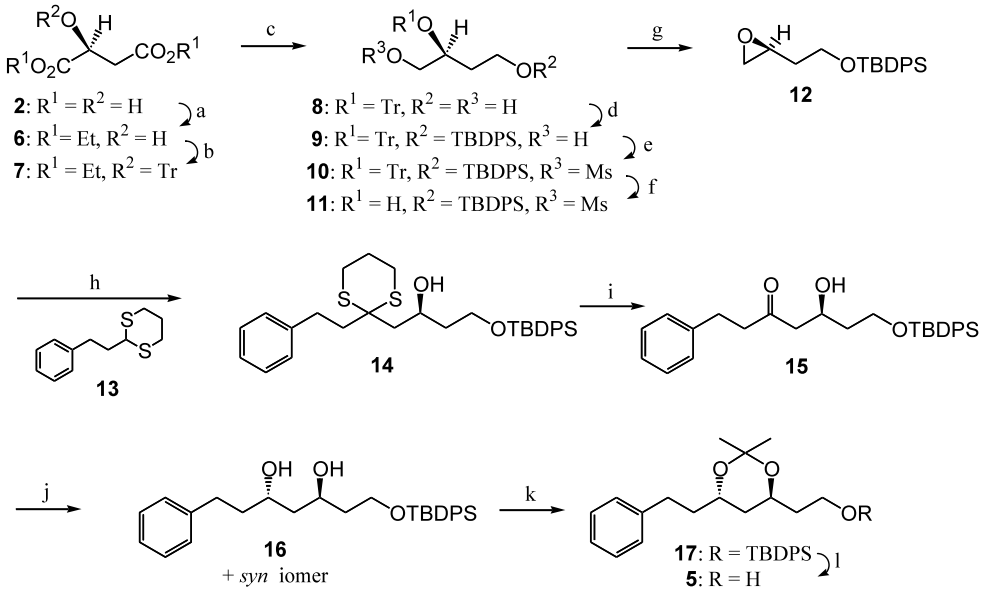


Scheme 1. *Reagents and conditions*: (a) OsO_4, $NaIO_4$, 1,4-dioxane–H_2O (3:1), rt, 45 min, 26%; (b) $NaBH_4$, EtOH, rt, 75 min, 66%.

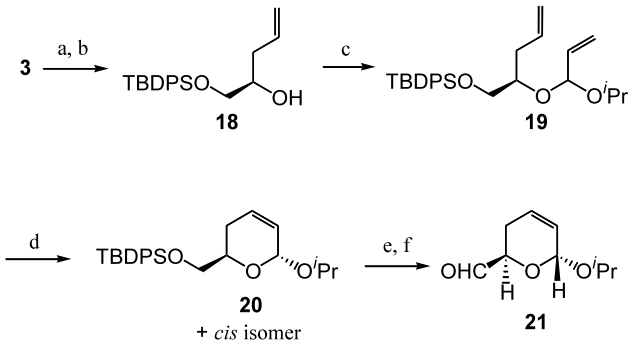
dioxane, and then the resultant aldehyde was reduced with $NaBH_4$ in EtOH to give primary alcohol (**5**), that exhibited $[\alpha]_D^{22}$ +26.8 (*c* 0.43, $CHCl_3$).

The synthesis of the two enantiomers of primary alcohol (**5**), which corresponded to the left-hand part of **1**, began with (*S*)- and (*R*)-malic acid, respectively, as illustrated in Scheme 2 (for simplicity, only the synthesis starting from the (*S*) form will be described here). Initially, a known chiral epoxide (**12**)[6] was prepared from malic acid in good yield by a newly developed process. In this synthetic route, the protection of the secondary alcohol with a trityl group enabled the regioselective silylation of one of two primary alcohols in **8**. The thus-obtained epoxide (**12**) was coupled with the anion generated from dithiane (**13**) to give secondary alcohol (**14**) in 98% yield. Deprotection of the dithioacetal group with I_2–$NaHCO_3$ in aqueous acetone yielded β-hydroxy ketone (**15**) in 77% yield. Stereoselective reduction was accomplished using $Me_4NHB(OAc)_3$[7] in acetonitrile–acetic acid (1:1) at −20°C, giving *anti*-diol (**16**) with excellent *anti*-selectivity (*anti*:*syn*= 99.2:0.8 by HPLC analysis). In order to confirm the relative configuration of 1,3-diol as well as to protect the diol function required for the following reactions, both *anti* and *syn* diols were transformed into the corresponding acetonide derivatives. The ^{13}C chemical shift of the two methyl groups in the acetonide part in **17** had almost the same values, namely, at δ 24.88 and 24.85 ppm, indicating that the two alcohol groups are in a 1,3-*anti* orientation.[8] In contrast, in the acetonide derivative prepared from a minor reduction product, signals were found at δ 19.93 and 30.44 ppm, which were characteristic for the methyl groups in the acetonide part of 1,3-*syn* diol.[8] The silyl protective group in **17** was removed by using TBAF in THF in the presence of 4 Å molecular sieves to afford primary alcohol (**5**) in 100% yield. The synthetic **5**, as well the ent-**5** derived from (*R*)-malic acid, were completely identical with **5** prepared from natural product described above, respectively, by comparison of their chromatographic behavior, as well as their spectral data (MS, ^1H and ^{13}C NMR data). Compound **5** and its antipode showed $[\alpha]_D^{25}$ +24.9 (*c* 1.7, $CHCl_3$) and $[\alpha]_D^{22}$ −21.9 (*c* 1.5, $CHCl_3$), respectively, demonstrating that the absolute configurations at C4′ and C6′ in **1** are *S*.

The right-hand part of **1**, i.e. the masked pyranone aldehyde (**21**), was synthesized from (*S*)-glycidol (**3**) according to the procedure of Crimmins et al.[9] with slight modification, as shown in Scheme 3. Two



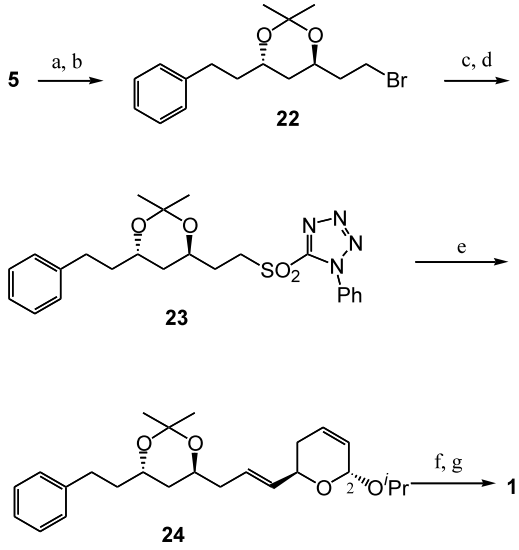
Scheme 2. *Reagents and conditions*: (a) conc. H_2SO_4, EtOH, reflux, 4 h, 93%; (b) Ph_3CCl, DBU, CH_2Cl_2, rt, 25 h, 71%; (c) $LiAlH_4$, Et_2O, reflux, 1.5 h, 88%; (d) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, −10°C, 72%; (e) MsCl, CH_2Cl_2, rt, 12 h, quant.; (f) BCl_3, CH_2Cl_2, −10°C, quant.; (g) K_2CO_3, MeOH, 0°C, 88%; (h) **13**, *n*-BuLi, THF, rt, 98%; (i) $NaHCO_3$, I_2, aq. acetone, 0°C, 77%; (j) $Me_4NHB(OAc)_3$, MeCN–AcOH (1:1), −20°C, 25 h, 95%; (k) 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2, rt, 3 h, 82%; (l) TBAF, 4 Å MS, THF, rt, 2 h, 100%.



Scheme 3. *Reagents and conditions*: (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 3 h, 67%; (b) vinylmagnesium bromide, CuI, THF, −25°C, 1 h, 88%; (c) acrolein diisopropylacetal, PPTS, 40→60°C, 32 h, 74% (diastereomeric mixture 1:1); (d) $RuCl_2(=CHPh)(PCy_3)_2$, CH_2Cl_2, reflux, 2 h, quant. (*trans*:*cis* 1:1, isolated *trans*-isomer 44%); (e) TBAF, THF, rt, 1 h, 87%; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl, −78°C, 10 min, 90%.

diastereomers obtained by ring-closing metathesis were separated by column chromatography and the *trans*-isomer (**20**) was used for further reactions.[10]

To achieve the total synthesis, Wittig olefination of aldehyde (**21**) with the triphenylphosphonium salt derivative prepared from bromide (**22**) was initially attempted; however, the desired olefinic product was obtained in very low yield. Then, the Kocienski-modified Julia olefination[11] was employed as follows. Bromide (**22**) was converted into the thiotetrazole in 96% yield, followed by oxidation with *m*-CPBA to give sulfone (**23**) in 96% yield. Next, the addition of NaHMDS to a solution of **23** and freshly prepared aldehyde (**21**) in THF at −60°C provided a mixture (4:1) of isomeric *E*- and *Z*-alkenes in 34% yield (Scheme 4). This mixture, which was difficult to separate



Scheme 4. *Reagents and conditions*: (a) MsCl, 2,6-lutidine, CH_2Cl_2, rt, 10 h, quant.; (b) LiBr, DMF, rt, 5 days, 86%; (c) 1-phenyl-5-mercaptotetrazole, NaH, DMF, rt→70°C, 96%; (d) *m*-CPBA, CH_2Cl_2, rt, 24 h, 96%; (e) **21**, NaHMDS, THF, −60°C, 1.5 h, 34% (*E*-, *Z*-isomer 4:1); (f) PPTS, acetone–H_2O (6:1), rt, 1.5 h, 80%; (g) MnO_2, pyridine, CH_2Cl_2, 24 h, 50%.

by column chromatography, was subjected to further reactions to complete the synthesis. Hydrolysis of the acetals at C2 and of the diol function with PPTS in aqueous acetone, followed by MnO_2 oxidation of the resulting allylic alcohol moiety gave the 5,6-dihydro-α-pyrone, which was recrystallized from *n*-hexane/$CHCl_3$ to afford the pure *E*-isomer in 30% overall yield. Synthetic **1** was completely identical in all respects (chromatographic behavior; mp (110–113°C); mass; IR; UV; CD; ^1H and ^{13}C NMR; $[\alpha]_D$) with natural strictifolione. Therefore, the structure including the absolute configuration of the three chiral centers in **1** was established.

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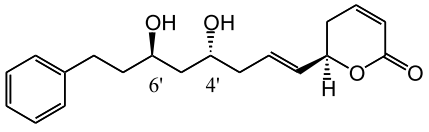

Figure 2.

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