Synthesis of the Stemodane Carbon Skeleton: Nonstereoselective Photoaddition of Allene to a Cyclopentenone and a Novel Rearrangement Reaction

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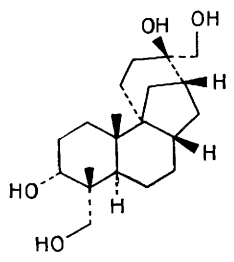
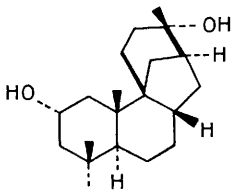
The tetracyclic dione (**21**), possessing the stemodane carbon skeleton, is obtained *via* an 8-step synthetic sequence from the tricyclic enone (**3**); the most interesting steps of the overall conversion involve the nonstereoselective photoaddition of allene to (**3**), and the transformation of both of the resultant adducts (**4**) and (**5**) into a *single* keto ester (**10**).

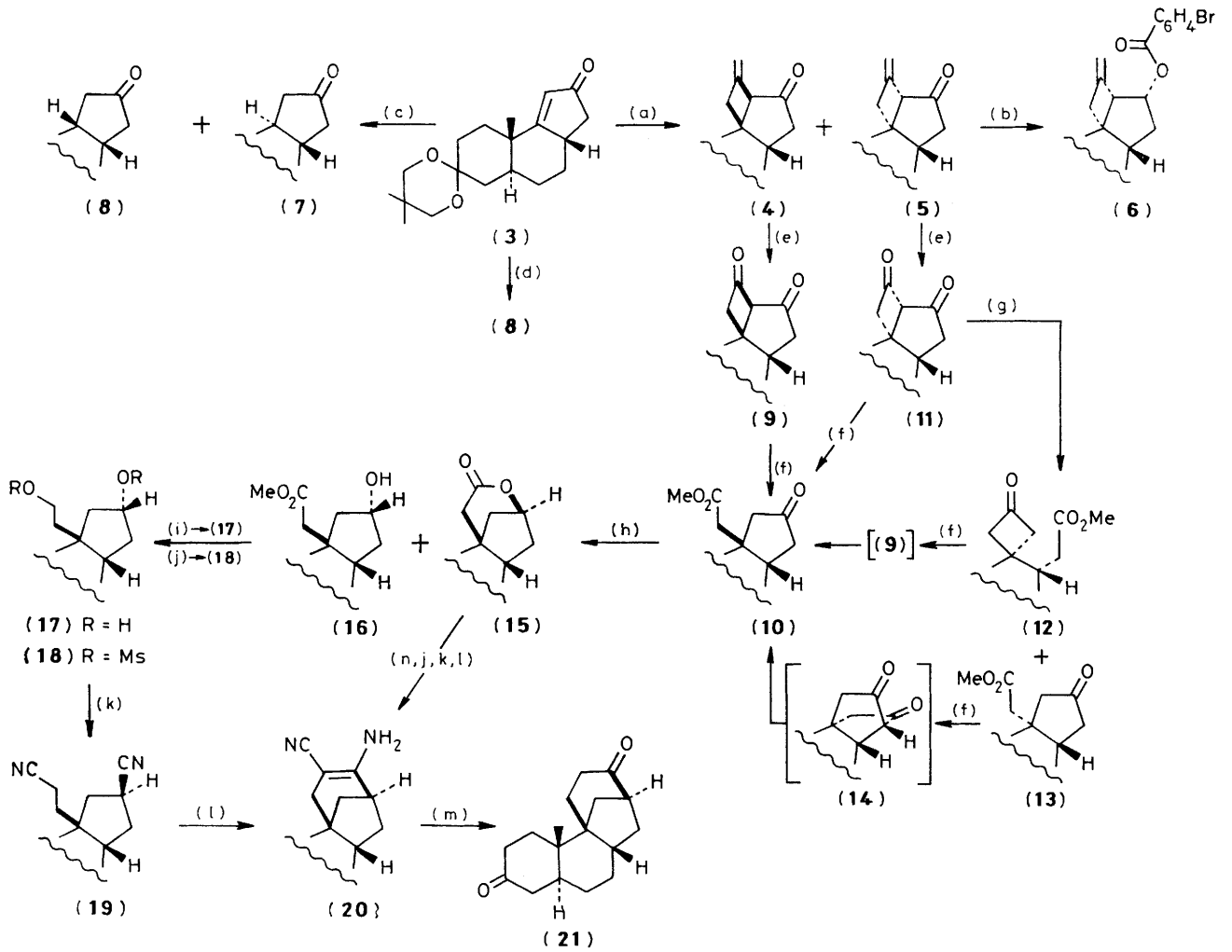
In connection with a research programme aimed at the total synthesis of the structurally and physiologically interesting diterpenoids aphidicolin (**1**)[1] and/or stemodin (**2**)[2], we report herein the following. (a) In contrast with comparable reactions involving simpler cyclopentenone systems[3] and a structurally very similar cyclohexenone,[4] the photochemical cycloaddition of allene to the tricyclic enone (**3**)[5] is nonstereoselective, providing the adducts (**4**) and (**5**) in nearly equal amounts. (b) Both (**4**) and (**5**) can be converted efficiently into the same keto ester (**10**), with the transformation of (**5**) into (**10**) involving a novel rearrangement reaction. (c) Compound (**10**) serves as a



(**1**)



(**2**)



Scheme 1. (a) $H_2C{=}C{=}CH_2$, tetrahydrofuran, *hν*, −78 °C; (b) $NaBH_4$, MeOH; *p*-bromobenzoyl chloride, pyridine; (c) Li, NH_3–ether, Bu^tOH; (d) H_2, Pd–C, MeOH; (e) O_3, CH_2Cl_2, MeOH (1.5 equiv.), −78 °C; Me_2S; (f) MeONa, MeOH, room temp., 2.5 h; (g) MeONa, MeOH, 0 °C, 5 min; (h) $LiBu^s_3BH$, tetrahydrofuran, −78 °C; (i) $LiAlH_4$, ether, room temp.; (j) $MeSO_2Cl$, pyridine, room temp.; (k) NaCN, hexamethylphosphoric triamide, 60 °C; (l) Bu^tOK, Bu^tOH, reflux; (m) H_3PO_4, HOAc, H_2O, reflux; (n) $LiAlH_4$, tetrahydrofuran, reflux. Ms = $MeSO_2$.

convenient precursor to the tetracyclic diketone (**21**), which possesses the stemodane carbon skeleton and which would appear to be an intermediate suitable for the total synthesis of (±)-stemodin and related natural products.

Irradiation of a tetrahydrofuran solution of allene and the enone (**3**)[5] (see Scheme 1)† provided a mixture of compounds (**4**) (39%, m.p. 134—135 °C) and (**5**) (42%, m.p. 132—134 °C), which could be separated by column chromatography on silica gel. The stereochemistry of each of these substances was determined unambiguously by *X*-ray analysis of (**4**)[6a] and of the *p*-bromobenzoate (**6**).[6b]

The stereochemical outcome of the photoaddition of alkenes to enones has been rationalized by Wiesner[3,7] on the basis of an empirical rule. Although a detailed discussion of the stereochemistry of cycloaddition of allene to (**3**) in terms of Wiesner's postulates is not appropriate here, it is pertinent to compare this reaction with the Li–NH_3 reduction of (**3**). Interestingly, the latter process provided a mixture of the isomeric ketones (**7**) (m.p. 90—91 °C) and (**8**) (m.p. 151—153 °C) in a ratio of *ca.* 7:3 (76% yield),‡ and, thus, these two reactions [(**3**) → (**4**) + (**5**); (**3**) → (**7**) + (**8**)] appear to provide support for the postulate[3,8] that it is legitimate to draw an analogy (in terms of stereochemical outcome) between the alkali metal–ammonia reduction of, and the photoaddition of an alkene to, an enone system.

Ozonolysis–reduction of the photoadduct (**4**), followed by treatment of the resultant unstable dione (**9**) with MeONa (catalytic amount)–MeOH (room temp., 2.5 h) gave the expected keto ester (**10**) (88%, m.p. 139—140 °C). Interestingly, subjection of (**5**) to an identical sequence of reactions provided an excellent yield of the *same* keto ester (**10**). In order to obtain information regarding the pathway of this unexpected transformation, the diketone (**11**) was subjected to MeONa–MeOH treatment under much milder conditions (0 °C, 5 min),§ which, remarkably, afforded the cyclobutanone (**12**) (33%, m.p. 157—158 °C) and the keto ester (**13**) (39%,

† All compounds shown in Scheme 1 [except (**9**) and (**11**), which are quite unstable, and (**14**), which is a presumed intermediate] exhibit spectral properties in accord with assigned structures and gave satisfactory molecular mass determinations (high resolution mass spectrometry).

‡ Hydrogenation of (**3**) provided only the ketone (**8**) (96%).

§ Treatment of (**9**) under these conditions gave only (**10**).

m.p. 156—157 °C) (separable by column chromatography), along with a small amount of (**10**). Treatment of either (**12**) or (**13**) with MeONa–MeOH at room temp. (2.5 h) produced [presumably *via* (**9**) and (**14**), respectively] the keto ester (**10**) in high yield.

The extraordinary conversion of (**11**) into (**12**) can be rationalized qualitatively as follows. Molecular models clearly show that the five-membered ring in (**11**) is quite strained, much more so than the corresponding ring in (**9**). The electrophilicity of the cyclopentanone carbonyl group in (**11**) is thereby increased (relatively speaking) and, therefore, methoxide attack at this site is competitive with attack at the similarly strained (although quite hindered) cyclobutanone carbonyl. The ready conversion of (**13**) into (**10**) must be rationalized on the basis of relative thermodynamic stability. Again, molecular models indicate that angle strain is considerably greater in the five-membered ring of (**13**) than in the corresponding ring of (**10**).

It should be noted that the mixture of (**4**) and (**5**) can be converted efficiently into the keto ester (**10**) (85%) without isolation of intermediates.

Reduction ($LiBu^{s}_{3}BH$) of (**10**) afforded a chromatographically separable mixture of the lactone (**15**) (23%, m.p. 194 °C) and the alcohol (**16**) (74%). Further reduction ($LiAlH_4$) of the latter substance, followed by mesylation of the resultant diol (**17**), provided the dimesylate (**18**) [80% from (**16**)]. Treatment of (**18**) with NaCN in warm hexamethylphosphoric triamide gave the dinitrile (**19**) (60%, m.p. 159—161 °C) which was converted smoothly *via* a Thorpe–Ziegler condensation[9] into the enaminonitrile (**20**) (90%, m.p. 213—215 °C). The latter substance could also be obtained by subjection of the lactone (**15**) to a sequence of reactions very similar to that employed for the conversion of (**16**) into (**20**).

Acid hydrolysis[10] of the enaminonitrile (**20**) afforded the diketone (**21**) (80%, m.p. 131—133 °C), which possesses the tetracyclic stemodane carbon skeleton. Investigations aimed at the conversion of (**21**) into (±)-stemodin (**2**) are underway.

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